(S)-γ-hydroxymethyl-α,β-butenolide (aka HBO), a Valuable Chiral Synthon: Syntheses, Reactivity and Applications

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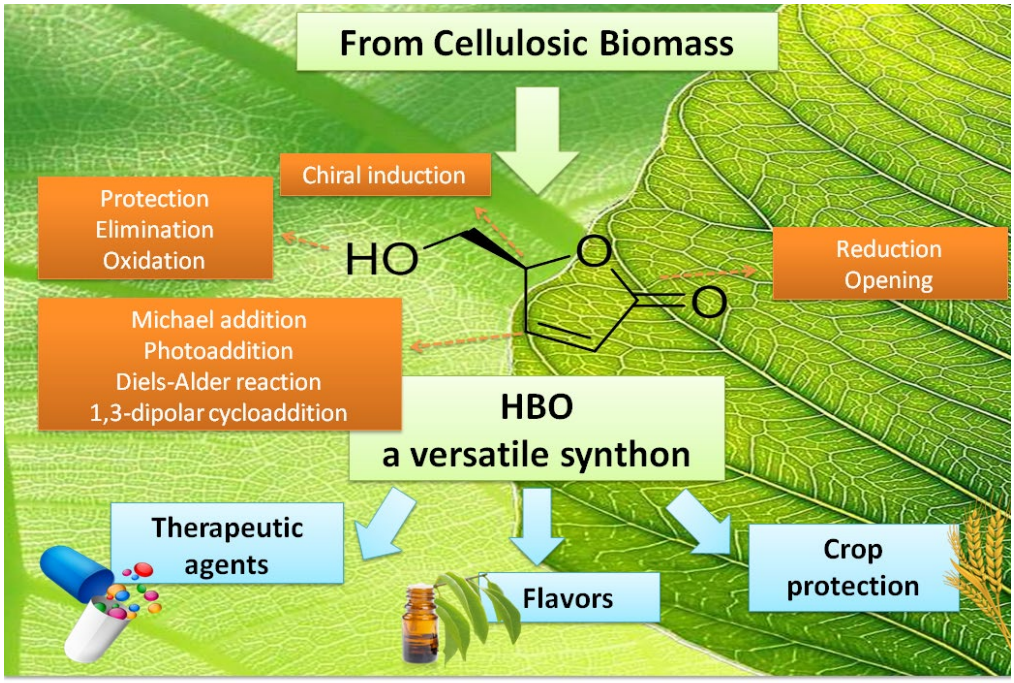
TOC


From Cellulosic Biomass
Chiral induction
Protection
Elimination
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Opening
Michael addition
Photoaddition
Diels-Alder reaction
1,3-dipolar cycloaddition
HBO
a versatile synthon
Therapeutic
agents
Flavors
Crop
protection

ABSTRACT Chirality is greatly sought for pharmaceutical compounds or fragrance and flavors. (*S*)-γ-hydroxymethyl-α,β-butenolide, aka **HBO**, is a chiral (*5H*)-furanone providing a polarized double bond, a lactone ring and a primary alcohol as playground for synthetic chemists. This molecule has been used for forty years in a wide range of synthetic pathways to natural and/or bioactive molecules. Its own synthesis, always from biosourced product, has also significantly evolved and could be now achieved both at large scale and by applying Green Chemistry principles. This review will explore the syntheses, the reactivity and the uses of **HBO.**

KEYWORDS (S)-γ-hydroxymethyl-α,β-butenolide, Levoglucosenone, Nucleosides, Photochemistry

INTRODUCTION

The global concept for bioeconomy is to develop new models ensuring the transition to a post-oil economy and the sustainable use of biological resources for food, feed, chemicals, energy and materials. For instance, one of the key target values is that 30% of overall chemicals production will be bio-based by 2030. For high added-value chemicals and polymers (specialties and fine chemicals), the proportion will be more than 50%. In this context, the need for bio-based platform molecules is constantly growing. A compound derived from biomass such as (*S*)-γ-hydroxymethyl-α,β-butenolide (**HBO**) - that possesses three functional groups, two unsaturations and a chiral center for only five carbons – would undoubtedly play an important role in the field of bio-based chemistry.

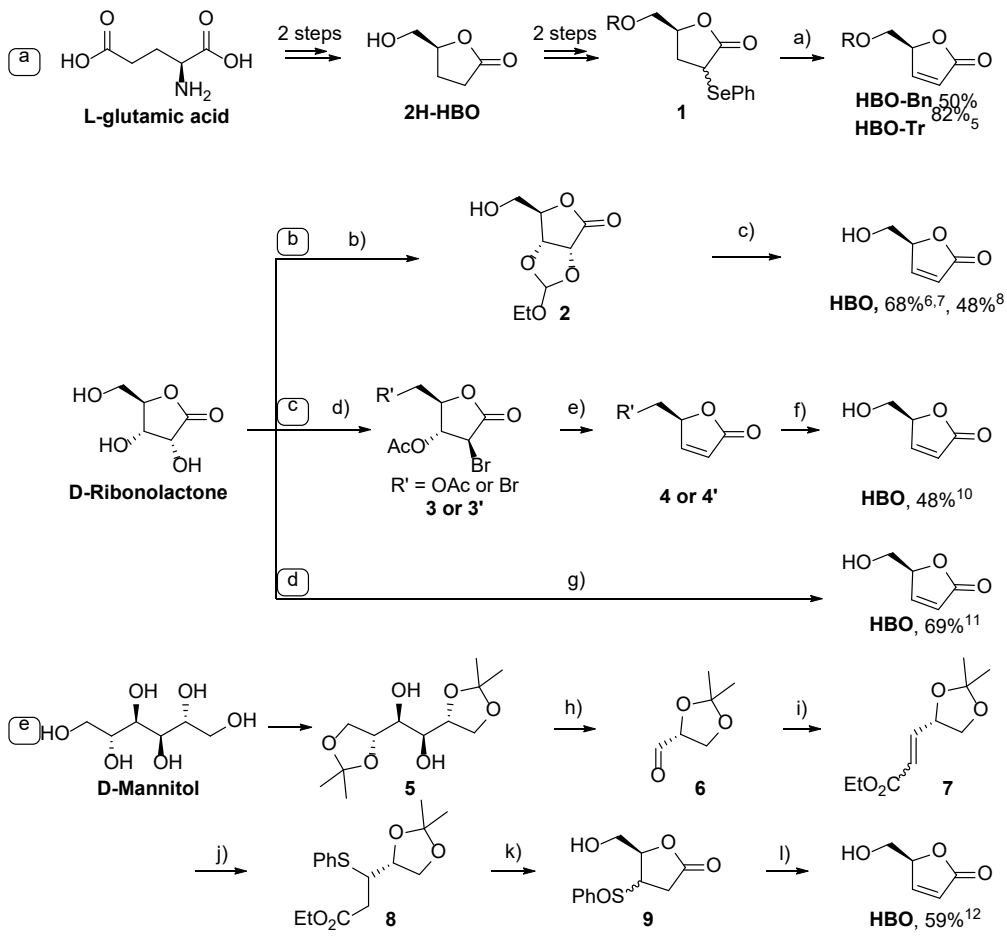
Since its first synthesis in 1979,[1] **HBO** was regularly used (about 20-30 publications per year) for both theoretical studies and total synthesis. The first ones have mainly dealt with the functionalization of the polarized double bond with regards to the chiral induction generated by

the hydroxymethyl group at the γ position. Additionally, **HBO** has been used in many synthetic pathways mainly to generate natural and/or pharmaceutical products. Such interest is wide spread around the world involving Japanese (15 publications), American (USA, Canada and South America, 13, 2 and 4 publications, respectively) or European research teams, in particular in Spain and France with 22 and 14 publications, respectively. It also remains constant from the beginning of the 80's with average 25 publications per decade. However, the use of **HBO** has been limited by its low availability resulting in a market price that was still recently of more than hundreds of dollars per gram.[2] Even if different pathways for its synthesis have been existing for more than thirty years, an economically viable and sustainable route is available only since last year, with a projected price below hundred dollars per kilogram, but remains to be industrialized yet.[3] In consequence, we believe that an overview of existing works performed on **HBO** would not only highlight the huge potential of this molecule but also could be an inspiration for new innovative works.

1. SYNTHESES OF **HBO**

At the end of the 70's, *O*-protected derivatives of **HBO** were synthesised with moderate to good yields (50-82%) in three steps – protection, phenylselenation and oxidation (with concomitant elimination) - starting from (*S*)-γ-hydroxymethyl-γ-butyrolactone, **2H-HBO** (Scheme 1a),[1,4,5] the latter derivating from L-glutamic acid through nitrous deamination and subsequent reduction of the carboxylic acid. Camps et al. proposed a new synthesis of **HBO** from D-ribonolactone in 1981, where only two steps were needed (Scheme 1b).[6,7] Acetal protection of the vicinal diols of ribonolactone with triethyl orthoformate was followed by pyrolysis to achieve the formation of the double bond leading to **HBO** in 68% yield but only at the limited scale of five hundred milligrams. Magnus et al. performed this procedure on nearly

15 g (0.1 mol), but with a significant decrease in yield (48%).[8] In 1983, Ireland and co-workers reported on a new methodology[9] not so far from the one described by Camps et al., where they formed an *O*,*O*-thiocarbonate instead of an acetal, starting from 5-*O*-tritylated ribonolactone. After treatment with Raney Nickel, tritylated **HBO** (aka **HBO-Tr**) was obtained in 51% yield at a multigram scale. Also starting from D-ribonolactone, Vekemans et al. described a three-step synthesis in 48% yield on multigram scale (Scheme 1c).[10] Treatment of the carbohydrate with HBr in acetic acid provided acetylated bromo-deoxyaldono-1,4-lactone, **3** or **3'**. Then, the $NaHSO_3$-mediated elimination of the acetate and bromide moieties led to the unsaturated lactone, **4** or **4'**, that was finally hydrolyzed under acidic conditions to provide **HBO**. More recently, Shimarizu and Toste used oxorhenium-catalyzed deoxydehydration to convert D-ribonolactone into **HBO** in only one-step with 69% of yield (Scheme 1d).[11] A third method was reported by Takano et al.,[12] using 1,2;5,6-di-*O*-isopropylidene-D-mannitol as starting material (Scheme 1e). First of all, an oxidative cleavage was performed and the obtained aldehyde **6** was submitted to a Wittig olefination (86% yield over the two steps). Then, thiophenol was added on the double bond and lactonisation was performed under acidic conditions. Treatment of the resulting intermediate with hydrogen peroxide afforded a sulfoxide group that can be eliminated to generate the double bond and give **HBO** (6 steps with an overall yield of 59%).



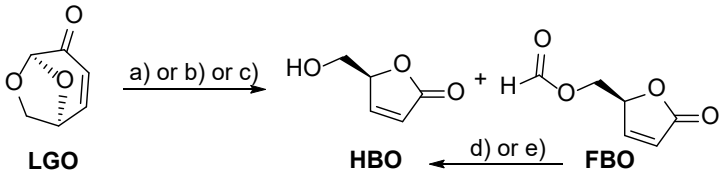
a) $NaIO_4$, 18-crown-6, $AcOEt/H_2O$, 50 °C, b) $HC(OEt)_3$, c) 200[8]-220[6,7] °C, 53 mbar, d) HBr, AcOH, 2 h, r.t., e) $NaHSO_3$, *i*PrOH, 72 h, r.t., f) HCl, MeOH, 18 h, r.t., g) CH_3ReO_3 (5 mol%), 3-pentanol, Ar, 155 °C, 2.5 h, h) $NaIO_4$, $NaHCO_3$, H_2O, 1 h, r.t., i) PhSh, *i*Pr_2NEt, benzene, 42 h, r.t., j) HCl, EtOH, 22 h, r.t., k) H_2O_2, AcOH, 2 h, r.t., l) $CaCO_3$, toluene, 3 h, reflux.

Scheme 1. Overview of historical syntheses of **HBO.**

Another renewable starting material for the production of (*S*)-γ-hydroxymethyl-α,β-butenolide is levoglucosenone, aka **LGO**, a chiral compound obtained through cellulose pyrolysis. Although it has been known for decades, **LGO** was generally obtained in very small quantities until an Australian start-up named Circa Group devised and optimized an extrusion-based process involving the flash pyrolysis of a mixture of sawdust and phosphoric acid in sulfolane (Furacell™ technology).[13] Initially validated at the benchscale, this process was then successfully implemented at the pilot scale and, currently, Circa is operating a 50 T/year **LGO**

production plant with Norske Skog Boyer in Tasmania. Until recently, two steps – Baeyer-Villiger oxidation and acidolysis – were necessary to convert **LGO** into **HBO** (Scheme 2). Conventional Baeyer-Villiger oxidation of **LGO** was first performed by Koseki's team in the early 90's using *m*-CPBA or peracetic acid as oxidants, followed by the methanolysis of the residual formate, **FBO**, achieved in methanol with catalytic amount of hydrochloric acid.[14,15] Even if this method provides **HBO** in average to high yields (65-90%), it is time consuming (48 h) and uses a peracid that is a hazardous reagent. Recently, Paris et al. suggested the use of metal-containing zeolites to perform the Baeyer-Villiger oxidation without any peracid.[16] Under such conditions, and after hydrolysis using acidic resin, up to 90% yield can be achieved. Best results were obtained with the tin-based zeolite; however potential residual toxic impurities (i.e., tin) could be a serious drawback for medical, food or cosmetic applications. To develop a safer and more efficient alternative, Flourat et al. were inspired by Kotlewska's[17] and Chavez'[18] works and exploited the ability of an enzyme, *Candida antarctica* Lipase B, aka CAL-B, to generate a peracid in situ from ethyl acetate. **HBO** was thus synthesized using a chemo-enzymatic process using H_2O_2 as oxidant, CAL-B as enzymatic oxidation mediator and ethyl acetate as both acyl donor and solvent.[19,20] After one variable at a time optimization, **HBO** has been obtained in good to excellent yields (90%) in only 8 h. It is noteworthy to mention that the use of a solid buffer not only further reduced the reaction duration (2h) but also allowed to reduce the enzymatic loading. Nevertheless, under such conditions, recyclability of the enzyme remained poor. An optimization by Design of Experiments using a Response Surface Methodology approach, was performed to determine the optimal operating conditions taking into account parameters interactions.[21] Results showed that antagonist conditions were required for the two key responses – yield and enzymatic

residual activity. So, it is impossible to simultaneously have good enzyme recyclability and a high yield.



Koseki's procedure: a) AcOOH, AcOH, Me_2S, 48 h, r.t.
d) MeOH, HCl, 45 °C, overnight. Yield 65 to 90%

Paris' procedure: b) Metal-zeolite, 100 °C, 4 to 48 h
e) Amberlyst-15, r.t. Yield 89%

Flourat's procedure: c) CAL-B, H_2O_2, AcOEt, HEPES, 40 °C, 2 h
e) Amberlyst-15, r.t. Yield 90%

Scheme 2. Syntheses of **HBO** from **LGO.**

In an attempt to find a cost efficient process, Bonneau et al. demonstrated that reacting **LGO** with only hydrogen peroxide proved to be very efficient as only **HBO** can be detected at the end of the reaction without the need of a hydrolysis step.[3] A study has then been developed to evaluate the correlation between reaction time *versus* the amount of H_2O_2 and selectivity towards **HBO**.[22] As safety and economical aspects were the priority, even if 95% yield in **HBO** can be achieved with an excess of hydrogen peroxide, the chosen conditions were: 0.98 equivalent of H_2O_2 - to avoid any post-treatment of the reaction - at 50 °C during 8 h. After purification of the crude reaction medium by molecular distillation, 72% of pure **HBO** were recovered on kilo-scale batches.

Comparison of the different published strategies for **HBO** production from **LGO** can be achieved by process mass intensity (PMI)[23] and Ecoscale[24] calculations. For PMI, in accordance with its definition, all the matter entering the process (reagents, solvents, treatment solution…), except water, is taken into account. The sum of theses masses necessary to produce 10 mmol of **HBO** is divided by the mass of 10 mmol of **HBO** (i.e., 1.141 g) (Table 1). In a second hand,

Ecoscale was calculated as described by Van Aken et al.[24] This indicator uses six categories to attribute penalty points to the process: yield, price, safety, technical setup, temperature/time and work-up/purification on the basis of 10 mmol production of the desired product. The sum of penalty is subtracted to 100 and gives the score of the Ecoscale (Table 1).

Table 1. PMI and Ecoscale for the different processes to converted **LGO** into **HBO**.

Process from	PMI	Ecoscale
Koseki et al. 1990	15.9	50.5[a]
Paris et al. 2013[b]	32.4[c]	55.5[a]
Flourat et al. 2014	22.7[d]	63/45.5[e]
Bonneau et al. 2018	1.96	75/68.5[e]

[a] Described procedure did not include workup and purification step. [b] Catalyst preparation was not considered. [c] Due to their recyclability, catalyst and Amberlyst-15 were not considered. [d] The calculation was based on two cycles procedure with a global yield of 67%. Hydrolysis procedure included Amberlyst/dioxane and as previously mass of Amberlyst was not taken into account. [e] Without/with purification step.

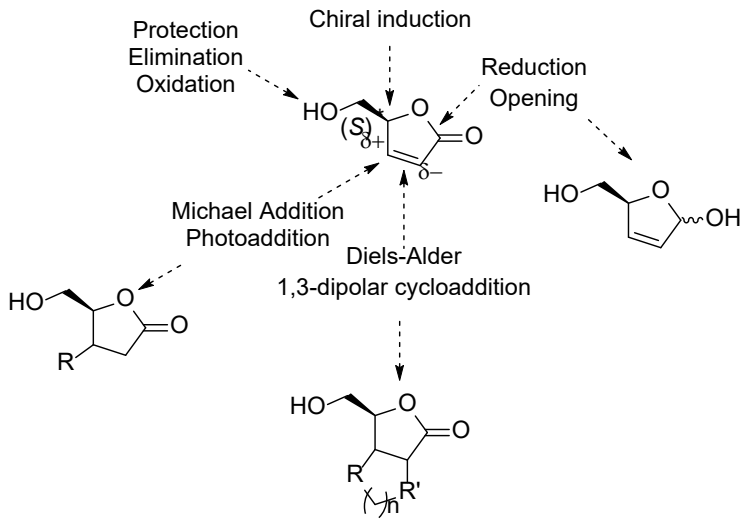
From Table 1, one can clearly see that the methodology developed by Bonneau et al. obtained the best scores. The very low PMI (less than 2), undoubtedly proves the efficiency of the process in terms of atom economy. PMI is mainly impacted by dilution factors. Indeed, when reagents are highly diluted in the media, the mass of solvent will be important. Koseki et al. have used concentrated media (2 $mol.L^{-1}$) in regards with Paris (0.33 $mol.L^{-1}$) and Flourat (0.75 $mol.L^{-1}$), explaining why their PMI was even quite low. In comparison, the Ecoscale neglects the waste generated by the process (only yield is considered), but is focused on the toxicity of the reagents and solvents used (safety) and on the energy used in the process (temperature/time and workup/purification). For the four procedures price, technical setup and temperature/time scores

were similar. The main difference was observed for the safety index, Paris et al. having achieved 35 penalty points due to the use of tin (15 pts) in dioxane (10 pts) with H_2O_2 (10 pts) whereas only H_2O_2 has been used in the Bonneau et al. procedure. It is worth mentioning that the purification process has also a huge impact on the final Ecoscale score. Indeed, even if the yield was better with Flourat's procedure before purification (82%), the cost of chromatography and the loss of product (-10 pts and final yield of 67%) led to a lower score compared to Bonneau's procedure where distillation was used for purification (-3 pts and yield from 78 to 72%).

To conclude, this comparison between different synthetic processes, all of them starting from bio-based **LGO** to produce **HBO**, highlights the huge impact of the chosen unit operations, reagents and solvents on both economical and environmental sustainability.

2. REACTIVITY STUDIES OF **HBO** AND ITS DERIVATIVES

Chirality and multifunctionality of **HBO** proved very useful tools for the synthetic chemist and have been often exploited to determine or induce stereo- or regioselectivity in different reactions (Scheme 3). The polarized α,β-unsaturated lactone has been extensively used to generate new carbon-carbon bonds. Additionally, these new bonds created a new asymmetric carbon and the selectivity can often be managed by playing with the nature of the protecting group on the hydroxymethyl moiety. The lactone ring can be reduced to afford an anomeric center or opened to generate epoxides for instance.

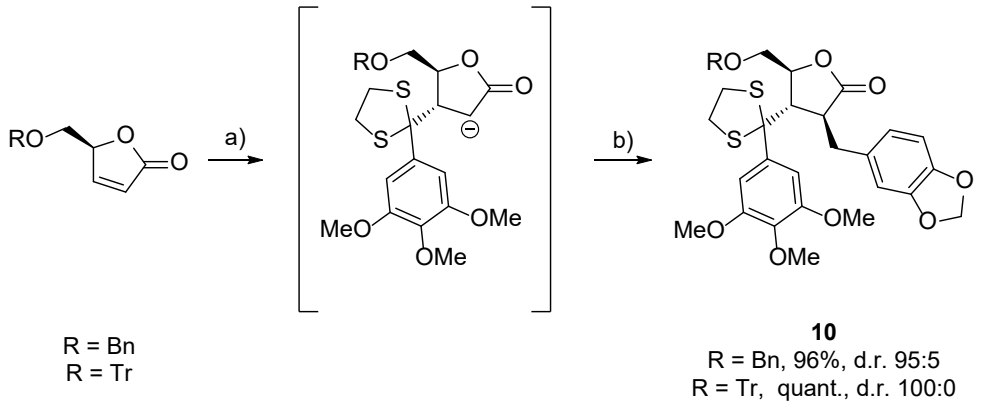


Scheme 3. Synthetic opportunities offered by **HBO**.

2.1 Michael addition (or 1,4–addition)

Michael addition consists in the creation of a C-C bond through the nucleophilic addition of a carbanion to α,β-unsaturated carbonyl functions. It has also been further extended to amine additions, aka Aza-Michael reactions.

Michael addition on benzyl-protected **HBO** (aka **HBO-Bn**) has been performed for the first time in 1979 in the synthesis of antileukemic lignans.[1] Tomioka et al. have added a trimethoxybenzaldehyde cyclic dithioacetal anion to the β-position of **HBO-Bn** followed by quenching with piperonyl bromide, obtaining 96% yield of product **10** with good purity (d.r. 95:5) (Scheme 4). In further investigations,[4,5] the same author has developed a similar approach to achieve the synthesis of steganacin, another antileukemia agent. The influence of the protecting group was highlighted by a total selectivity for the *anti*-addition when a trityl substituent was used. Additionally, the subsequent S_{N2} process on piperonyl bromide was also completely stereoselective, *anti* compared to the first addition intermediate (Scheme 4).



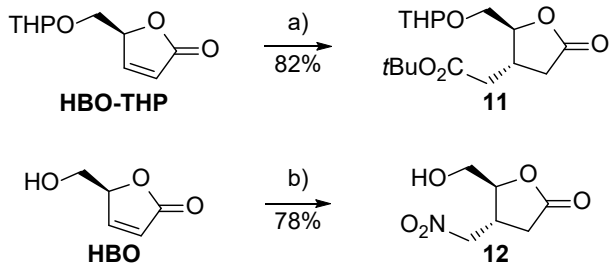
R = Bn
R = Tr

10
R = Bn, 96%, d.r. 95:5
R = Tr, quant., d.r. 100:0

a) Lithio trimethoxybenzaldehyde dithioacetal, THF, -78 °C, 3 h, b) Piperonyl bromide, THF, -78 °C to r.t., 15 h.

Scheme 4. Selective addition of trimethoxybenzaldehyde cyclic dithioacetal to **HBO-Bn** and **HBO-Tr** followed by *anti* addition of piperonyl bromide.

Nagaoka et al. have also used Michael reaction on the tetrahydropyranylated **HBO** (aka **HBO-THP**) in their synthesis of (+)-Mayolide A.[25] *tert*-Butyl acetate was deprotonated using LDA and reacted on **HBO-THP** with high stereoselectivity and in good yield (82%, Scheme 5). The *anti* stereoselectivity was also perfectly controlled in Rosso's and Pilli's work for nitromethane addition to **HBO** (78% yield) (Scheme 5).[26]

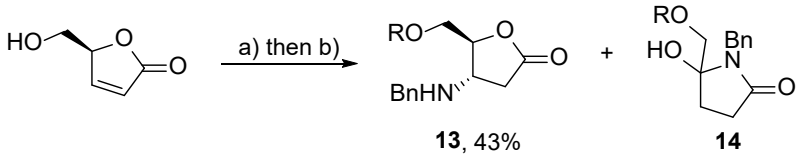


a) *t*BuOAc, LDA, THF, -78 °C, b) CH_3NO_2, DBU, 4 h, r.t.

Scheme 5. Michael additions reported by Nagaoka et al.[24] (top) and Rosso and Pilli[25] (bottom).

Various aza-Michael reactions were performed on **HBO** and related derivatives. Chu et al. have obtained β-azido pseudo nucleosides by addition of lithium azide on **HBO**.[27,28] Noteworthy,

the bulkiness of the protecting groups (*tert*-butyl dimethyl silyl, aka TBDMS or *tert*-butyl diphenyl silyl, aka TBDPS) ensured a total *anti* selectivity. To access β-aminoesters or lactams, Collis et al. have added benzylamine to **HBO** (Scheme 6).[29,30] In this particular example, the presence of a protecting group (TBDPS) led to poor yield of reaction (21-26%) due to partial deprotection (55-65% of silanol recovery), and consequently they have performed the aza-Michael addition directly on **HBO** (performing the protection thereafter in order to purify the target molecule, **13**), the global yield over the two steps being 43%. It is noteworthy to mention that the *anti* selectivity was total even without any protecting group. The moderate yield could be explained by the formation of a by-product due to rearrangement into an amide, **14**.

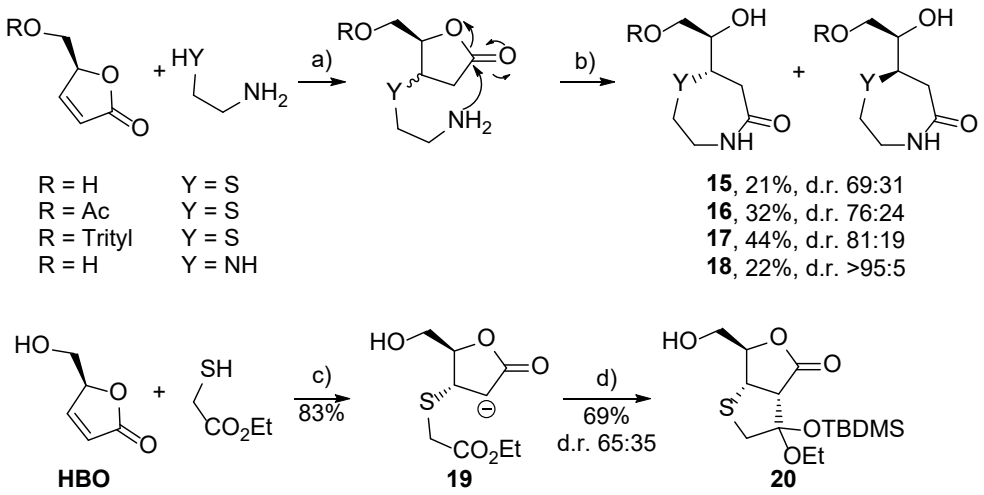


13, 43% **14**

a) $BnNH_2$, MeOH, 0 °C, 24 h, b) TBDMSCl or TBDPSC, Im., DMF, r.t., 48 h.l

Scheme 6. Aza-Michael addition of benzylamine on **HBO**.

Hydrazines additions were realized by Bohrisch and co-workers on (*R*)-γ-hydroxymethyl-α,β-butenolide, the enantiomer of **HBO**,[31,32] and after addition to the β-position on the less hindered face, rearrangement occurred to afford hydroxyalkyl-pyrazolidinones. The same group has performed several Michael-type additions on **HBO** and **HBO** derivatives such as acetylated **HBO**, aka **HBO-Ac**, or tritylated **HBO**, aka **HBO-Tr**, using diverse 1,4-bis-nucleophiles, such as diamines, thio-amines,[33] or ω-thiohydroxyesters.[34] The initial nucleophilic addition occurred mainly following an *anti* fashion but not exclusively, followed by a ring transformation. With ω-thiohydroxyesters, a bicyclic compound, **20**, could be obtained under specific conditions (TBDMS-triflate/triethylamine) (Scheme 7).



a) DMF, r.t., 6 h, b) EtMgBr, THF, Ar, r.t., 3 h or cysteamine, H_2O, 80 °C, 15 min then r.t. 3 h,
c) Et_3N, DMF, Ar, r.t., 3 to 7 h, d) Et_3N, THF, Ar, TBDMSOTf, - 78 °C, 2 h then r.t. 5h.

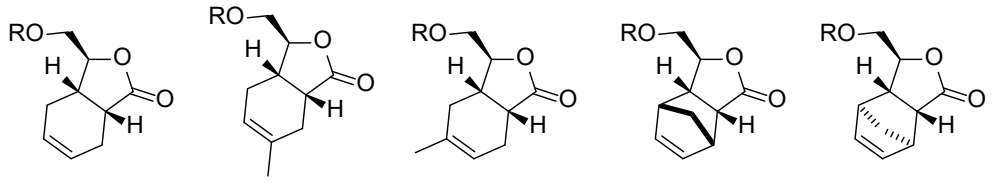
Scheme 7. Michael addition of 1,4-bisnucleophiles to **HBO** and ring rearrangement.

2.2 Diels-Alder reactions

The Diels-Alder reaction ([4+2] cycloaddition), is a widely used method in organic chemistry to create cyclic derivatives by reaction of an alkene (also called dienophile), with a diene. In our particular case, **HBO** or its protected forms on primary hydroxyl group of **HBO** were applied as dienophiles.

To the best of our knowledge, the first mention of Diels-Alder reaction on protected **HBO** has been reported by Mann and Thomas with the simplest possible diene, butadiene.[35] Only one product, **21** (Chart 1) has been observed in 75% yield after one week of reaction. While Mann and Thomas have performed a Lewis acid-mediated Diels-Alder reaction, one year later, Ortuno et al. reported on thermal Diels-Alder reactions on various chiral butenolides (Table 2, entries 1-5).[36] They have also observed only one product for the addition of butadiene, confirming the stereoselectivity of the reaction directed to the less hindered face of the butenolide (*anti*), even with none (**HBO**) or a small protecting group (methylated **HBO**, aka **HBO-Me**) (Table 2, entries 2 and 4). Noteworthy, yields were low when **HBO** or **HBO-Ac** have been used as starting

materials, due to degradation (by elimination of water or acetic acid) (Table 2, entries 2 and 3). To progress further in the understanding of regioselectivity of Diels-Alder reaction on butenolides, the same group investigated the cycloaddition of isoprene under both thermal and catalytic conditions.[37] They have observed the same total diastereofacial selectivity than with butadiene. Noticeably, no regioselectivity appeared under thermal conditions (125 or 220 °C), giving a 1:1 mixture of *para/meta* regioisomers, **22** and **23** (Chart 1) (Table 2, entry 1), whereas under catalytic conditions ($AlCl_3$, 50 °C) performed on (*S*)-γ-methyl-α,β-butenolide, **MBO**, the *para*-regioisomer **23** was favoured (with a 80:20 ratio, Table 2, entry 9). They pursued their investigation with cyclopentadiene with both thermal and catalytic conditions (Table 2, entries 10-16).[38–40] In the thermal process, the major product was identified as the *endo* adduct, **24** (Chart 1). However, increasing reaction temperature led to a decrease in the *endo*/*exo* ratio from 3.5 at 30 °C to 2.3 at 125 °C along with an increased global yield (Table 2, entries 10-12). The authors have concluded that the attack of the diene was possibly controlled by kinetic parameters in their range of temperature. Lewis acid-mediated catalysis (using zinc halides) favored the *endo* addition directly on **HBO**, reaching an impressive 15:1 ratio, and a drastically increased yield, up to 95% (Table 2, entries 14-16). They have selected this methodology to produce a valuable intermediate **26**, involved in the syntheses of several carbocyclic nucleosides such as antibiotics or antiviral agents (Scheme 8).[41] In a related study, Moraes et al.[42] have used a thermal procedure at 100 °C leading to a 80:20 *endo/exo* mixture in 82% yield before epoxidation and determination of absolute configuration.



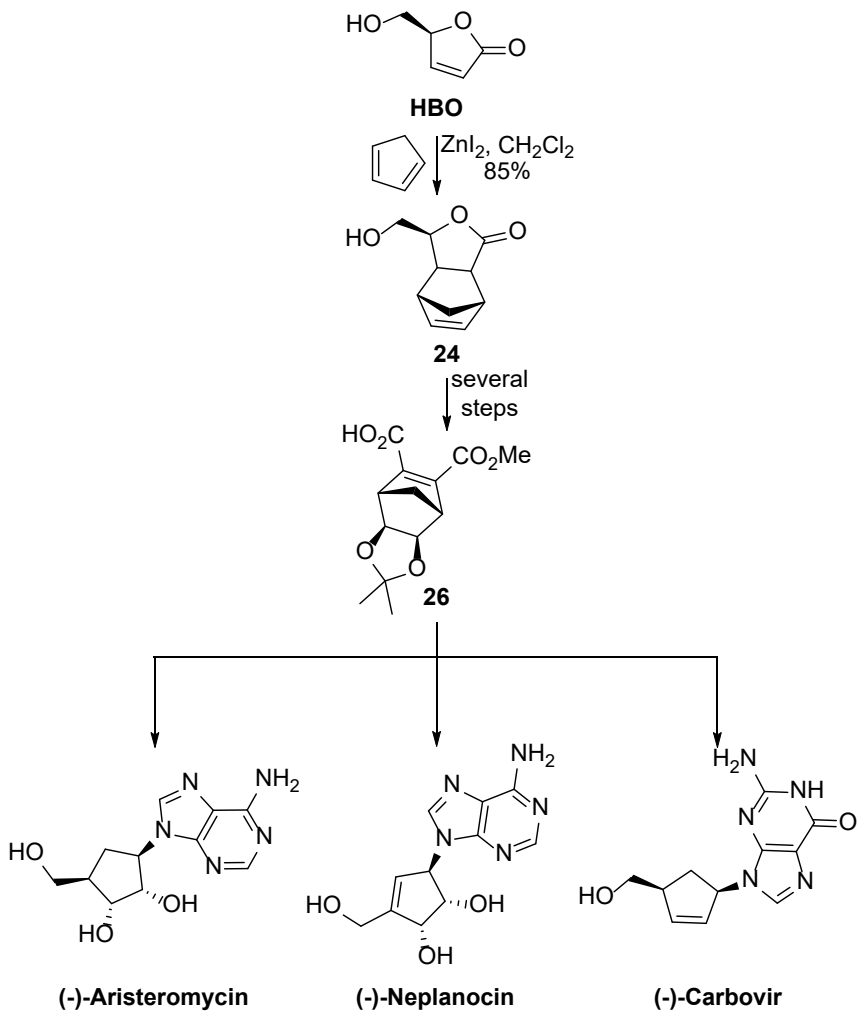
21 **22** **23** **24** **25**

Chart 1. Products of Diels-Alder reaction of **HBO** derivatives and butadiene (**21**), isopropene (**22** and **23**) or cyclopentadiene (**24** and **25**).

Table 2. Diels-Alder reactions on various butenolides.

Entry	Butenolide	Diene	Temp (°C)	Time (h)	Catalyst (equiv.)	Yield (%)	Ratio *para*/*meta* or *endo*/*exo*
1	**MBO**[a]	Butadiene	210	21	-	70	-
2	**HBO**[a]	Butadiene	210	21	-	32	-
3	**HBO-Ac**[a]	Butadiene	210	21	-	53	-
4	**HBO-Me**[a]	Butadiene	210	21	-	77	-
5	**HBO-Bn**[a]	Butadiene	210	21	-	80	-
6	**MBO**[b]	Isoprene	200	20	-	80	1:1
7	**HBO-Bn**[b]	Isoprene	220	20	-	52	1:1
8	**HBO-Bn**[b]	Isoprene	125	20	-	52	1:1
9	**MBO**[b]	Isoprene	50	48	$AlCl_3$ 0.33	42	8:2
10	**HBO-Bn**[c]	Cyclopentadiene	30	-	-		3.54:1
11	**HBO-Bn**[c]	Cyclopentadiene	73	-	-		2.85:1
12	**HBO-Bn**[c]	Cyclopentadiene	135	-	-		2.33:1
13	**MBO**[d]	Cyclopentadiene	20	21	$ZnCl_2$/$EtAlCl_2$ 0.4/0.2	72	11:1
14	**HBO**[d]	Cyclopentadiene	35	8	$ZnCl_2$	55	15:1
15	**HBO**[d]	Cyclopentadiene	35	7	$ZnBr_2$	72	10:1
16	**MBO**[a]	Butadiene	210	21	-	70	-

[a] Ref35 [b] Ref36 [c] Ref37 [d] Ref39



Scheme 8. HBO transformation into platform molecule **26**, precursor of nucleosides.

Diels-Alder reactions were not restricted to ester or alkyl-derivatives of **HBO**, and were also successfully implemented for the synthesis of silylated compounds under Lewis acid-mediated catalysis.[43–46]

Diels-Alder reactions on **HBO** or protected **HBO** occur always following a totally diastereofacial anti selectivity. Consequently, the orientation of the newly induced stereogenic centers is known. Additionally, for other dienes, such as isoprene or cyclopentadiene, regioselectivity or stereoselectivity can be oriented by controlling key parameters such as temperature, time and Lewis-acid catalytic species.

2.3 Studies of 1,3-dipolar cycloadditions

1,3-dipolar cycloaddition is a [3+2] cycloaddition between a dipole, such as nitrones or diazo compounds, and a dipolarophile, **HBO** and derivatives in this review. Interest for the mechanism and selectivity of 1,3-dipolar cycloadditions on **HBO** began in the mid-90's, even if the first attempt was reported in 1985,[35] this reaction being used regularly thereafter in total syntheses.[47,48]

Baskaran and co-workers performed 1,3-dipolar cycloadditions of diazomethane[49] and nitrones[50,51] on α,β-unsaturated esters and lactones. HOMO and LUMO energies of **HBO** were calculated using the semi-empirical method called AM1, obtaining -10.86 and -0.47 eV respectively in order to understand the behaviour of such dipolar additions. From their experiments, it seemed that the approach of a dipole occurred only from the less-hindered face - anti - and regioselectively by the addition of the negatively charged part of the dipole on the β carbon of the unsaturated lactone (Chart 2: **27** and **28**). In the case of *N*-(benzylidene)methylamine *N*-oxide, two isomers were produced with a 1.2:1 ratio, due to a low stereoselectivity with this substituted nitrone (Chart 2: **29** and **30**).

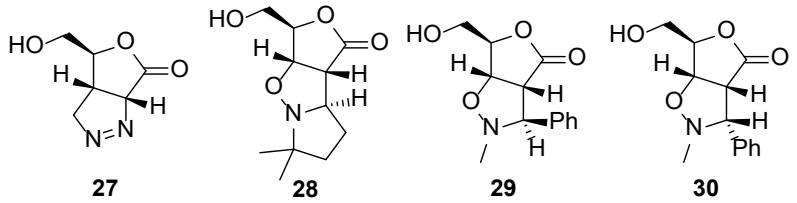
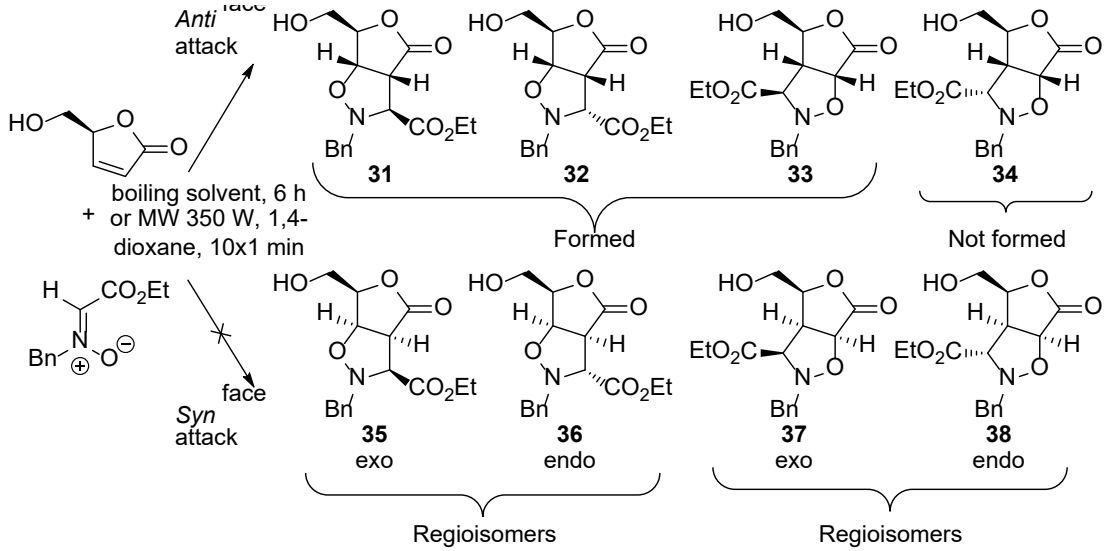


Chart 2. Products of the 1,3-dipolar addition of diazomethane (**27**), 2,2-dimethyl-3,4-dihydro-2H-pyrrole *N*-oxide (**28**) and *N*-(benzylidene)methylamine *N*-oxide (**29** and **30**) to **HBO.**

Ondrus et al.[52] have observed that the facial selectivity was total for the addition of *N*-benzyl-*C*-ethoxycarbonyl nitrone on **HBO**. On the other hand, no total regioselectivity was achieved. On the eight possible products (Scheme 9), three products have been observed, as a mixture of **31**,

32 and **33**. Ratio between the different products varied depending of the solvent (i.e. benzene: 53:37:10 ; CH_2Cl_2: 30:56:14). The method used to establish the absolute configurations relies on NMR analysis (NOESY and COSY). These absolute configurations were achievable only because an enantiopure initial synthon was used, here **HBO** which is a pure *S* form. Another attempt, using microwave irradiation in 1,4-dioxane, improved slightly the selectivity to give a ratio of 64:23:10, but also generated 3% of the *anti* product **35**. In order to efficiently increase the selectivity towards the *exo*-product, playing with the bulkiness of the protecting group proved to be a good strategy, and provided ratio of 64:25:11 and of 83:15:2 with acetate or TBDPS groups, respectively.



Scheme 9. The eight possible products from the 1,3-dipolar addition of *N*-benzyl-*C*-ethoxycarbonyl nitrone to **HBO.**

Between 2006 and 2009, Stecko et al. have published a series of articles dedicated to the selectivity of nitrones addition to unsaturated lactones in prolonged times transformations (40-50 h) (Chart 3).[53–56] Main results are reported in Table 3. With an achiral cyclic nitrone **39**, three products were formed from **HBO**, *exo-anti/exo-syn/endo-anti* (78:7:15). These results are in

agreement with energies calculated for this exothermic reaction. When **HBO** was silylated with a bulky protecting group (TBDPS), the *exo-syn* product was not detected and *exo-anti* began to be even more predominant. They have also investigated the 1,3-dipolar addition of chiral cyclic nitrones on **HBO**. When respective steric hindrances of each compound did not oppose, i.e. matching pairs (Table 3, Entry 3) the selectivity for *exo-anti* was total. In contrary, mismatched pairs (Table 3, Entry 4) provided three products and the *endo-anti* isomer was obtained as major product due to the clutter of *exo*-face. In addition, they have shown that a prolonged heating can influence the ratio of products, suggesting that the reaction is reversible. However, assays to achieve thermodynamic products, by using extended reaction times and higher temperatures, led to undesired racemization of the compounds. With chiral nitrones bearing two substituents, when the function present on α position of the new bond corresponds to the matched configuration, the observed selectivity remains total for *exo-anti* (entry 5). If this first substituent acts as a mismatch compared to **HBO** chirality, the three usually observed products were recovered but with a lower selectivity (Table 3, Entry 6). In the case of a compound substituted at the β position of the new bond, when the configuration was favourable, only the two *exo* products are formed (Table 3, Entry 7), and when β-position is occupied by a substituent in disfavourable configuration, *exo-syn* and *endo-anti* products are obtained (Table 3, Entry 8). In summary, contrary to the Diels-Alder reaction, the reversible 1,3-dipolar addition does not show any preference for *endo*-addition.

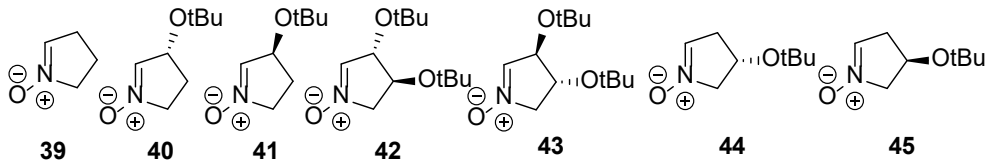
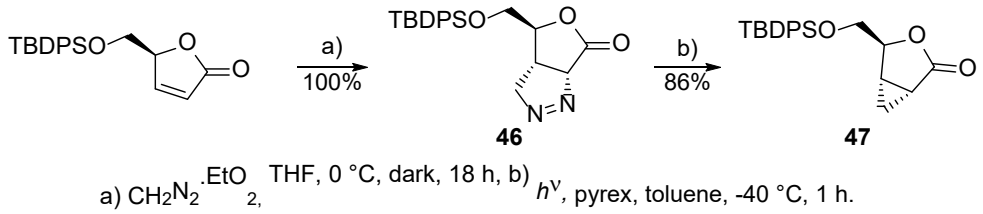


Chart 3. Structures of nitrones used by Stecko et al.

Table 3. Selectivity of 1,3-dipolar addition of achiral and chiral nitrones on **HBO** and **HBO-TBDPS** reported by Stecko et al.

Entry	Butenolide	Nitrone	*Exo-anti*	*Exo-syn*	*Endo-anti*
1	**HBO**	**39**	78	7	15
2	**HBO-TBDPS**	**39**	94	0	6
3	**HBO**	**40**	100	0	0
4	**HBO**	**41**	27	21	52
5	**HBO**	**42**	100	0	0
6	**HBO**	**43**	45	32	23
7	**HBO**	**44**	79	21	0
8	**HBO**	**45**	0	73	27

The observed total facial selectivity was also successfully implemented for the production of cyclopropane adducts, such as **47**, after photolysis of the pyrazoline compound **46**, obtained from 1,3-dipolar cycloadditions of diazomethane on **HBO** derivatives (Scheme 10).[48,57]



Scheme 10. Transformation of protected **HBO** into cyclopropane adducts.

2.4 Photochemistry on **HBO**.

Absorbing light (photon), molecules reach specific electronically excited states corresponding to precise electron distributions, leading to original chemical properties and reactivities. As photochemical reactions generally occurred without additional reagents, the byproduct formation is dramatically reduced, revealing photochemistry as a high-potential approach in green

chemistry.[58–60] Photoadditions of alcohols,[61–67] acetals[62,65,68,69] or amines[70] to **HBO** have been reported in the literature.

Primary and secondary alcohols did not react in the same way under irradiation. Secondary alcohols are able to directly form a stable radical whereas primary alcohols need intermediate species to achieve the desired transformation. Indeed, radical species derived from a primary alcohol were generated by hydrogen abstraction mediated for example by excited triplet state benzophenone.[63] In all described examples, the addition occurred at the β position of butenolides. The facial selectivity, determined using Mosher esters analysis, demonstrated that the adduct was *anti* regarding to the hydroxymethyl moiety.[63] Chart 4 shows molecules obtained after irradiation of **HBO** with two secondary alcohols, isopropanol and cyclopentanol (**48**[61] and **49**[66]), or on diverse protected **HBO** (**HBO-TBDMS, HBO-Ac** and 4,4'-dimethoxytrityl, aka **HBO-TMD**) with methanol (**50**,[63] **51**[62] and **52**[67]) and ethylene glycol (**53**[65]). In this last example, no yield was reported by Brown and co-workers.[65]

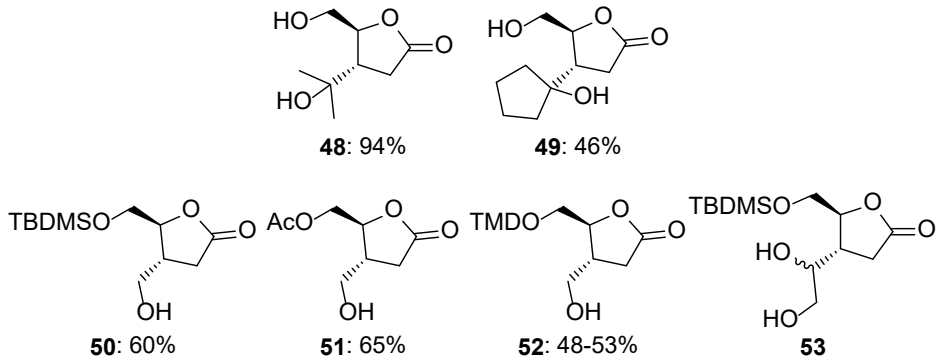


Chart 4. Products of the photoaddition of alcohols to **HBO** and derivatives.

Photoaddition products on **HBO** derivatives could also be obtained with acetals such as dioxolane. In a first approach, moderate yields were observed (40 and 54% from 2,2-dimethyl-1,3-dioxolane on **HBO-TBDMS** and 1,3-dioxolane on **HBO**, respectively).[62,65] Ghost et al. have optimized the photochemical addition of 1,3-dioxolane to diverse protected **HBO** derivatives

(**HBO-Bn**, **HBO-TBDMS**, **HBO-Ac**, pivaloylated **HBO**, aka **HBO-Piv**, benzoylated **HBO**, aka **HBO-Bz** or tetrahydropyranated **HBO**, aka **HBO-THP**), increasing yields up to 93% yield (Table 4).[68] It is worthy to mention that the presence of *syn* adducts in small quantities were observed.

Table 4. Results of photoadditions performed by Ghost et al. with 1,3-dioxolane on **HBO** derivatives.

Butenolide	Ph_2CO (%)	Temp (°C)	Time (h)	Yield (%)	*Anti*/*Syn* ratio
HBO-Bn	10	0	9	82	96:4
HBO-TBDMS	150	20	45	36	76:24
HBO-TBDMS	10	6	12	87	96:4
HBO-Ac	8	6	6	91	96:4
HBO-Piv	11	6	5	93	97:3
HBO-Bz	15	6	3	80	96:4
HBO-THP	15	20	6	91	96:4
HBO	10	0	4	80	97:3

To the best of our knowledge, the photoaddition of amines to **HBO** was only reported by Santiago de Alvarenga and Mann.[70] Irradiation of *tert*-butyldimethylsilyl protected **HBO**, with *N*-methylpyrrolidine in acetonitrile provided two diastereomers in *anti* relationship with the TBDMS protected hydroxymethyl moiety of **HBO** (Chart 5, structures **54** and **55**). The demethylation of the resulting adducts proved unsuccessful, and consequently authors have investigated the photoirradiation of **HBO-TBDMS** and **HBO-Me** with *N*-(trimethylsilyl)pyrrolidine. After subsequent treatment of the resulting adducts with potassium

tert-butoxide, azabicyclo compounds were isolated in 15-20% yields (Chart 5, structures **56** and **57**).

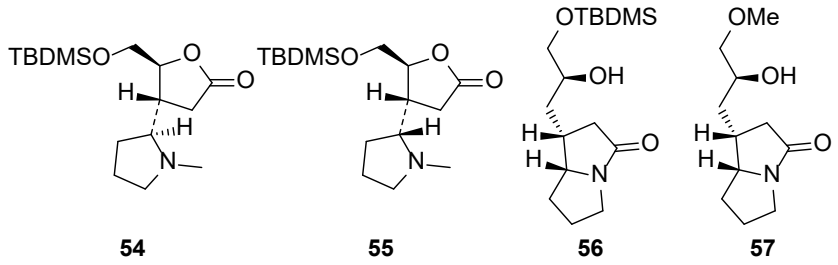
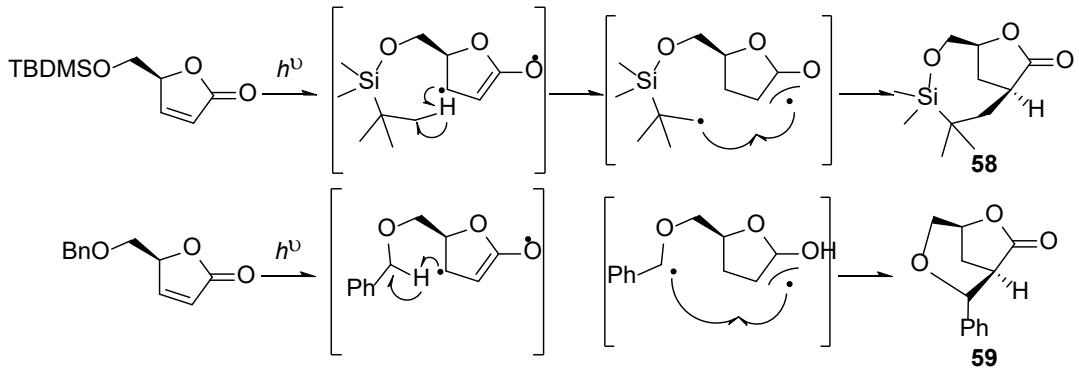


Chart 5. Products of the photoadditions of amines to **HBO** derivatives.

An intramolecular reaction can also be performed under irradiation of protected **HBO**, Brown et al. having reported on the intramolecular cyclization of **HBO-TBDMS**,[65] suggesting a mechanism where hydrogen abstraction from the *tert*-butyl moiety by the radical located in β-position led to the subsequent addition to the α-position, creating a constrained bicyclic compound, **58** (Scheme 11). Noticeably, Alibès and co-workers have observed the same behaviour with benzylated **HBO** (Scheme 11).[71]

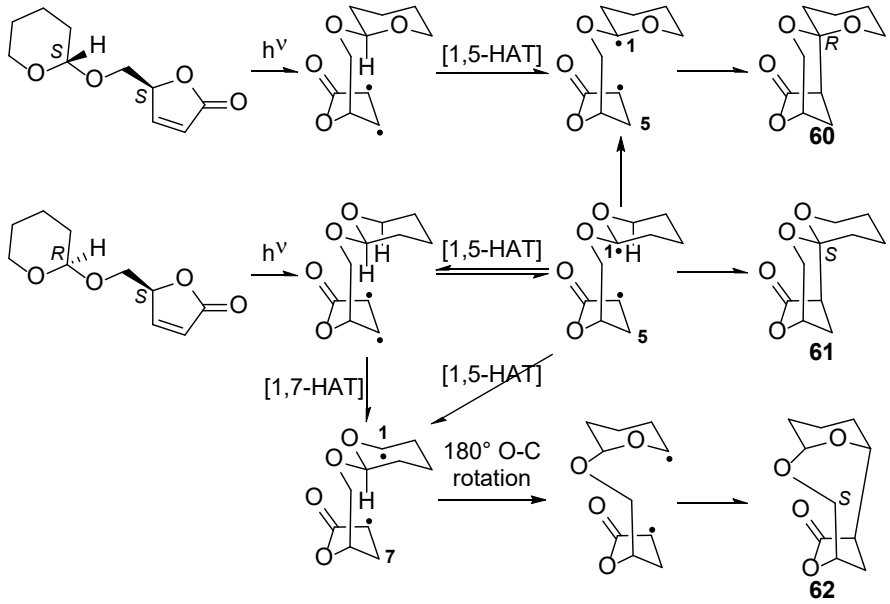


Scheme 11. Suggested mechanism for the intramolecular cyclization of **HBO-TBDMS** and **HBO-Bn** under irradiation.

This intramolecular photoreaction was then implemented on a panel of **HBO** derivatives to elegantly access tetrahydropyrans.[72] From simpler derivatives (i.e., benzyl, methyl, *n*-butyl, aka

But and isopropyl, aka *i*Pr), by playing with solvent and reaction time, the desired products were obtained in moderate to good yields (38-78%). Configuration of tetrahydropyran of **HBO-But** was resolved by ^{1}D NOESY as (*1R,2S,5S*). With more complex **HBO** derivatives (i.e., MEM- or vinyl ether protections), mixtures of various unidentified regioisomers presumably resulting from [2+2] cycloadditions were obtained.

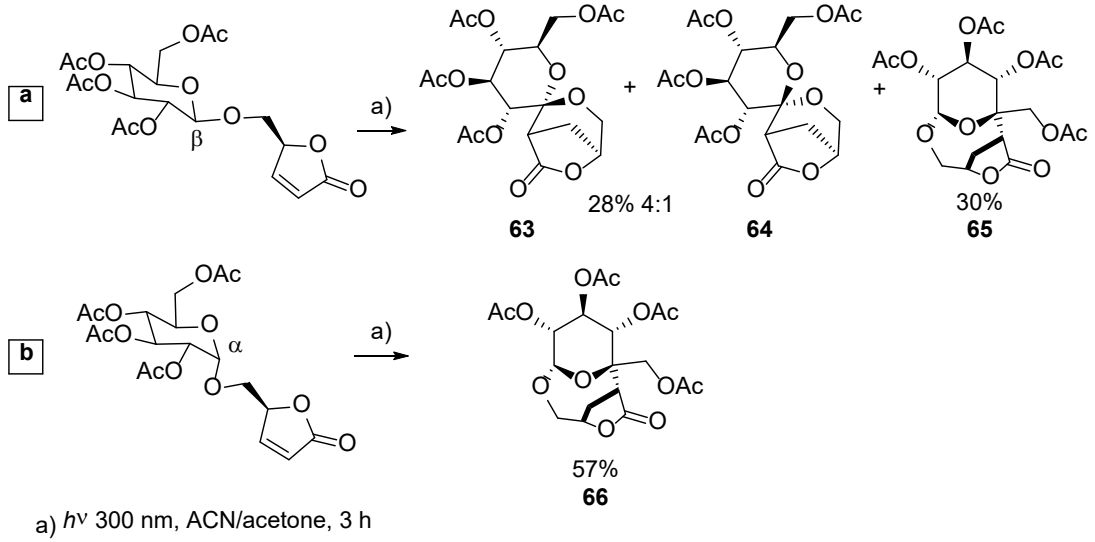
HBO-THP (epimeric mixture) was also studied, results being similar to those obtained by Jahjah et al.[73] Although the experimental conditions were not exactly the same as previously tested, Alibès and Jahjah proposed the same mechanism to explain the formation of such compounds: hydrogen abstraction in 1,5 and 1,7-positions and subsequent intramolecular cyclization (Scheme 12).



Scheme 12. Mechanism of the hydrogen abstractions involved in the synthesis of tetrahydropyrans.

Jahjah et al.[73] have also explored the α-selectivity of intramolecular photoadditions of *O*-acetylated glucosides of **HBO**. Hydrogen abstraction could occur at the anomeric position but

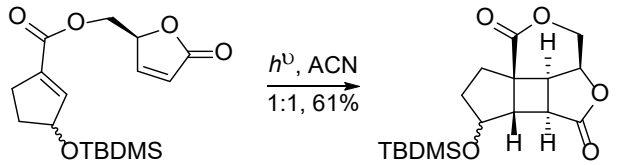
also at the 5 position on the D-glucose moiety. In their study, cycloaddition starting from the β-anomer led to three isolated products (Scheme 13a, structures **63**, **64** and **65**). Moreover, the new C-C bond between the α-carbonyl of the lactone and the anomeric C1 of D-glucose showed a α:β anomeric ratio of 4:1. For the third product, the new C-C bond was formed between the α-carbonyl of the lactone ring and C5 position of D-glucose. Interestingly, it has been noticed that the initial β-anomer could be transformed to the α-anomer. Starting from the *O*-acetylated-α-glucosides of **HBO**, the third compound **66** was the only observed product (Scheme 13b). From these results, it was assumed that an epimerisation occurs once the radical is formed. It was also demonstrated that the relative configurations of the starting materials significantly drives the regioselectivity of the hydrogen abstraction, and thus the overall stereoselectivity of the reaction.



Scheme 13. Products of photoirradiations of *O*-acetylated glucosides of **HBO** in β-configuration (a) and α-configuration (b).

[2+2] Photocycloadditions of **HBO** derivatives have also been investigated to synthesize cyclobutane moieties and access natural and/or bioactive molecules.

The first [2+2] photocycloaddition on a derivative of **HBO** was described in 1985 in the course of the synthesis of stoechospermol. In this work, an intramolecular reaction between the double bond of the α-β-unsaturated lactone and an α,β-unsaturated ester introduced on the hydroxymethyl moiety was performed (Scheme 14).[74]

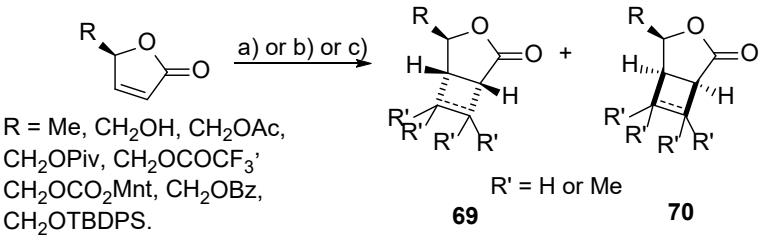


67 **68**

Scheme 14. First internal [2+2] photocycloaddition of a **HBO** derivative.

Six years later, Alibès and co-workers have added simple alkenes (e.g., ethylene and tetramethylethylene) to various derivatives of **HBO**, their main objective being the study of the facial selectivity (Scheme 15 and Table 5). They have observed that *anti*-adducts were favored even in the reaction between ethylene and (*S*)-γ-methyl-α,β-butenolide, **MBO**. So, steric effects were not the only factor affecting selectivity suggesting that stereoelectronic effects could also influence the facial selectivity. Authors' hypothesis was a n-π interaction between oxygen's non-bonding electrons of the hydroxymethyl moiety (activated when linked to a carboxyl protection) and π-orbitals of the butenolide double bond. The same group has extended its investigation using acetylene.[75,76] Yield and selectivity were quite similar to those obtained with ethylene (Table 5), even with methoxycarbonyl or benzoyl moieties where different steric hindrances were expected. The lower yield observed for **HBO-Bz** was attributed to a photoreduction of the cyclobutene to cyclobutane (Scheme 16a), whereas with **HBO-TBDPS**, only decomposition has been observed. For another silylated compound (**HBO-TBDMS**), Brown and co-workers[65] have described the formation of homodimers **75** and **76** in acetonitrile under irradiation at 254 nm through [2+2] photocycloaddition between the double bonds of two butenolides (Scheme 16b).

Cyclobutene ring can also be obtained by the photocycloaddition of (*Z*)-1,2-dichloroethylene and subsequent dehalogenation (Scheme 16c).[77]

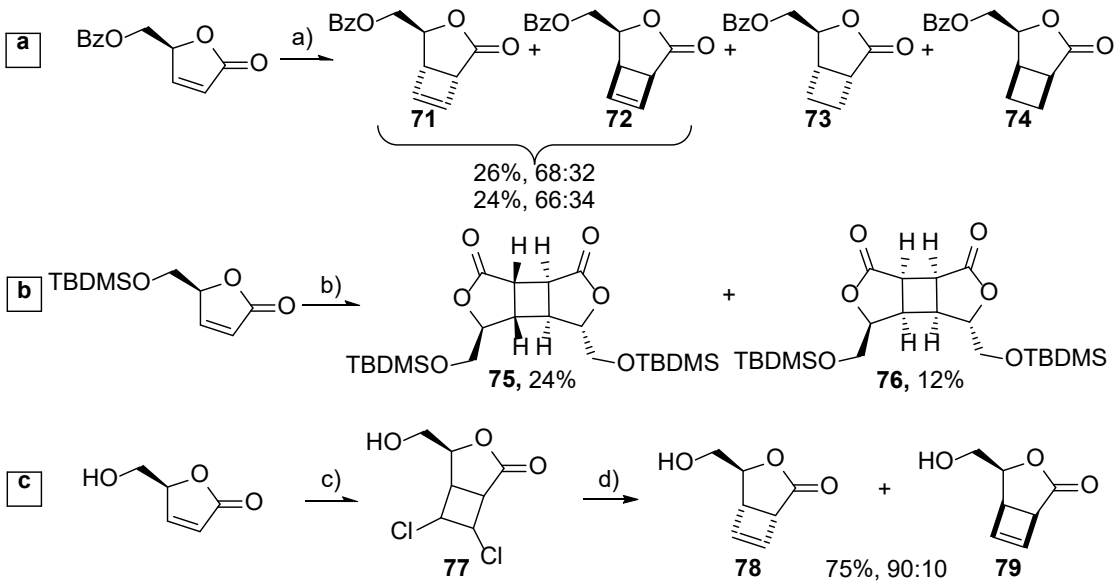


a) $h\upsilon$, ethylene, b) $h\upsilon$, TME, c) $h\upsilon$, acetylene

Scheme 15. General procedure of [2+2] photocycloaddition between various γ-substituted butenolides and olefins.

Table 5. Ratios and yields for cycloadducts depending on the substituents on the γ-position of the butenolide and the olefin. Adapted from ref 70 and 72.

Butenolide	Alkene/Alkyne	Yield (%)	*Anti*:*Syn* ratio
MBO	Tetramethylene	37	73:27
HBO		42	74:26
HBO-Ac		40	78:22
HBO-Piv		44	82:18
HBO-COCF$_3$		20	80:20
MBO	Ethylene	48	59:41
HBO-Ac		46	74:26
HBO-Piv		19	78:22
HBO-Piv	Acetylene	44	70:30
HBO-CO$_2$Mnt		42	66:34

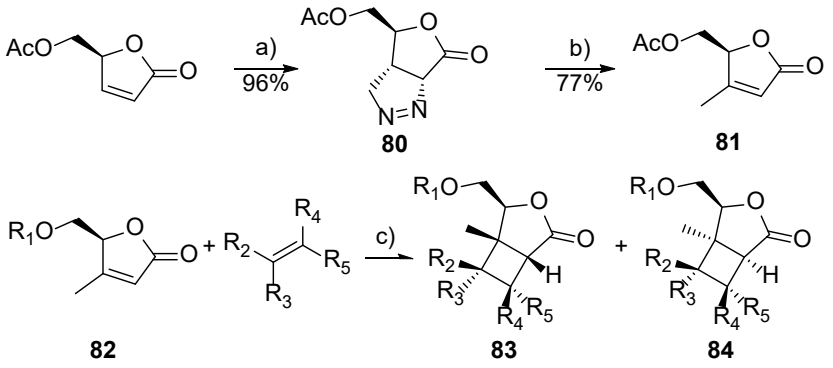


Scheme 16. [2+2] photoaddition of (a) acetylene on **HBO-Bz**, (b) **HBO-TBDMS** on itself and (c) (*Z*)-1,2-dichloroethylene on **HBO**.

Alibès et al. have also applied these [2+2] photoadditions approaches to synthesize cyclobutane-fused nucleosides as new potent anti-HIV agents.[78]

They have also investigated the impact of a substituent on the double bond in [2+2] photocycloadditions, using this strategy to devise an elegant synthetic route to (+)-grandisol, a sexual pheromone of the Boll weevil. Their first observation was a decrease in facial selectivity when ethylene was added to a double bond carrying a methyl group in the β-position.[79] In 1996, the same team has published a more detailed article, using different alkenes and reaction conditions but with only a methyl in β-position as a substituent on **HBO-Piv** (Table 6, Entries 2-11) excepted for entry 1 where methyl was positioned on **HBO-Ac** (Table 6, Scheme 17).[71] Although temperature did not govern the facial selectivity, it influenced significantly the yield (Table 6, Entries 2-4). The generally accepted mechanism evolving through 1,4-biradicals, which

could explain the formation of an additional product in the case of tetramethylethylene, was agreed and detailed. Regarding olefin/solvent interaction, electron-richest olefins reacted better under direct irradiation (ether/quartz) whereas electron deficient olefins required sensitization by π-π* triplet generated in acetone (a pyrex filter being used to avoid any decomposition). In 2003, Alibès et al. have also performed assays with acetylene (Table 6, Entries 12-13) leading to moderate yield and low selectivity.[76]



a) CH_2N_2. Et_2O, THF, -5 °C then r.t., 48 h, b) Dioxane, reflux, 51 h, c) $h\upsilon$

Scheme 17. Synthesis of β-methylated **HBO-Ac** (top) and synthesis of various fused cyclobutanes by [2+2] photocycloaddition between protected β-methylated **HBO** and olefins (bottom).

Table 6. Yields and selectivities of the [2+2] photoadditions of olefins to β-methyl-**HBO-Piv.**

Entry	Alkene	Temp (°C)	Solvent	Filter	% Desired product	*anti*:*syn*	% Other product
1	Ethylene	-45	acetone	Pyrex	65	55:45	n.d.
2		-78	acetone	Pyrex	Quant.	62:38	n.d.
3		-45	acetone	Pyrex	70	62:38	n.d.
4		-15	acetone	Pyrex	60	62:38	n.d.
5		-48	acetone	Quartz	10	60:40	n.d.
6	TME	25	ether	Quartz	28	79:21	17

7		25	ether	Quartz	13	77:23	8
8		-20	ether	Quartz	37	78:22	25
9		25	acetone	Pyrex	6	83:17	3
10	Vinylene carbonate	-78	acetone	Pyrex	54	88:12	n.d.
11		-78	Ether	Quartz	<2	n.c.	n.d.
12	Acetylene	20	acetone	Pyrex	32	54:46	detected
13		20	ether	quartz	44	53:47	detected

Rustullet et al. have studied the regioselectivity of [2+2] photoadditions, adding 1,1-diethoxyethylene on **HBO** derivatives.[80] The ratio of the four possible isomers *anti*:*syn* and head to tail (HT):head to head (HH) (Chart 6) were evaluated, and correlated with (1) the bulkiness of the protecting groups, (2) the position of the methyl substituent on the double bond (α- or β-positions), and (3) the nature of the solvent (i.e., acetonitrile, diethyl ether or *n*-hexane). Concerning this last parameter, the use of acetonitrile, a polar aprotic solvent, resulted in a good yield in moderate time and stereoselectivity, whereas diethyl ether and *n*-hexane, which can be both considered as non polar aprotic solvents, provided a better regioselectivity but worse facial selectivity. For these two solvents, where regioselectivity was high (>90:10 HT:HH), the position of methyl group did not reveal any impact, contrary of what can be observed in acetonitrile, where the presence of a β-methyl strongly increased the HT:HH ratio from 78:22 to 94:6, while α-methyl enhanced just slightly this parameter (80:20). Moreover, the bulkiness of protecting groups had low impact on facial selectivity and none on regioselectivity.

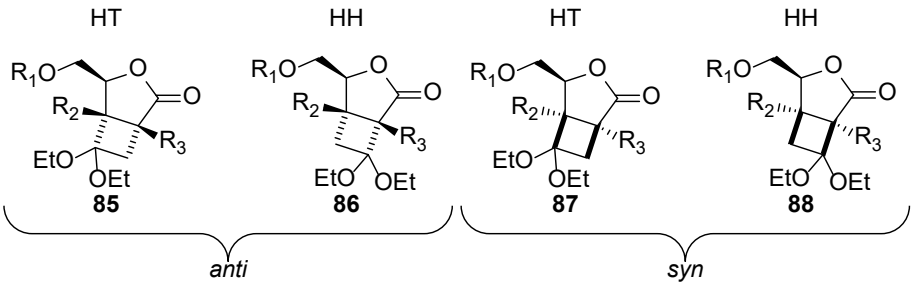
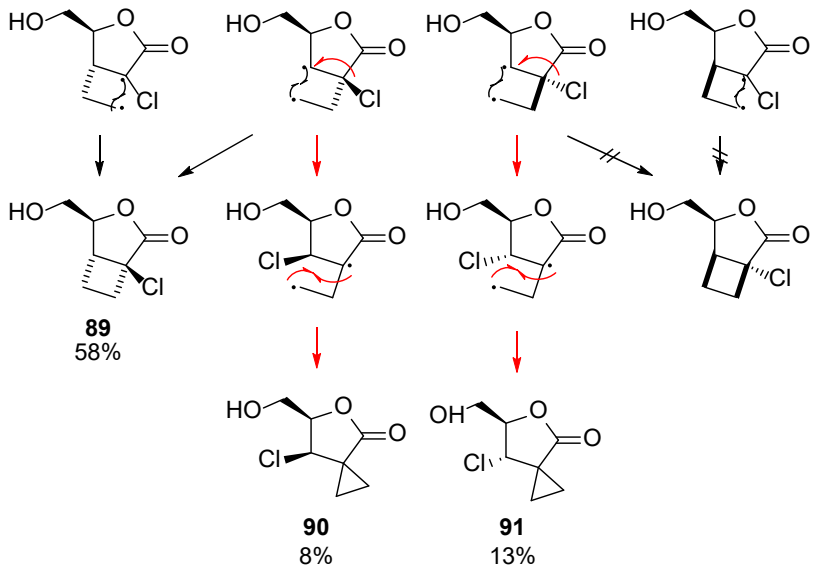


Chart 6. Products of [2+2] photoadditions of 1,1-diethoxyethylene to **HBO**.

Finally, in 2011, the same research group has explored the reactivity of **HBO** derivatives bearing halogen moieties (i.e., Cl or F) on α-position of the double bond (Scheme 18).[77] In the case of ethylene addition to the fluoro-adduct, the yield (80%) and the selectivity (81:19) were improved, in comparison with reactions with **HBO** (66%, 66:34), whereas the chloro-adduct gave three different products, the *anti*-adduct **89** in 58% yield and two spirocyclopropyl derivatives, **90** and **91**, obtained through chlorine migration from α to β-position, followed by ring closure. [2+2] photocycloadditions of acetylene to the same substrates gave lower yields (53, 28 and 17% respectively from **HBO**, 2-fluorobutenolide and 2-chlorobutenolide). Although fluorine did not lead to higher yield with acetylene, it did improve the selectivity going from 65:35 with **HBO** to 95:5 with the fluorinated compound. As previously described, no *syn*-adduct was detected starting from chloro-derivatives. The low yields could be explained by the secondary photoactivity on the new double bond formed after acetylene addition, resulting in the presence of tricyclic products.



Scheme 18. Mechanism of formation of spirocyclopropyl derivatives from [2+2] photoadditions of ethylene to α-chloro-**HBO**.

In 2003, this research group has also investigated [2+2] photocycloadditions of **HBO**, synthesized from D-mannitol.[76,81] *Anti* selectivity was favored and can be enhanced by playing with the protecting group. With ethyl and benzyl groups, rearrangements occurred leading to pyrans **95** and **96**, as previously observed (Chart 7).

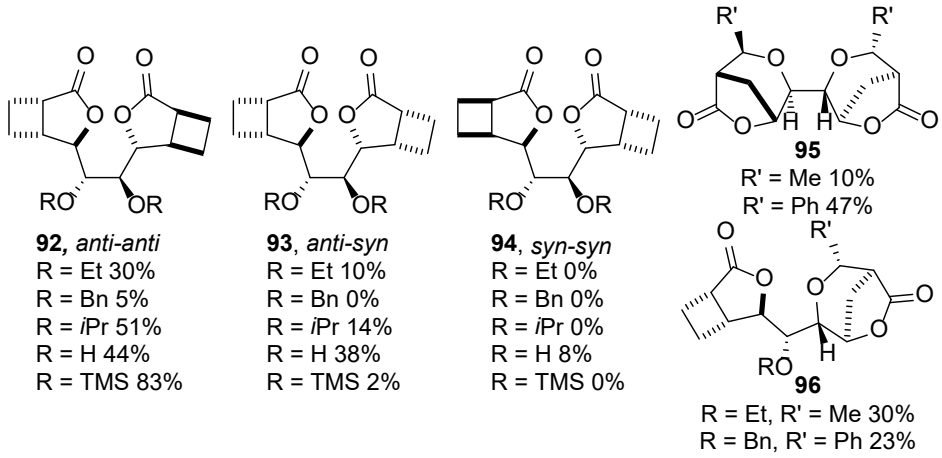


Chart 7. Products of ethylene photoaddition on **HBO** dimers.

This team continued its effort, with a recent publication dedicated to an intramolecular [2+2] photocycloaddition.[82] Xin et al. have described the formation of polyfunctionalized cyclobutanes from **HBO** with a protecting group bearing itself a double bond. Previous work has already shown that [2+2] photocycloaddition occurred with vinyl-substituted derivatives.[72] First of all, they have tested terminal alkenes with different temperatures and solvents. To achieve good yields and selectivities, acetone proved to be the best solvent at -78 °C. Due to an intramolecular constraint generated by the stereogenic center, only the photoaddition *syn* adducts could be isolated following this methodology. Regioselectivity regarding HT and HH structures ratios was greatly influenced by the chemical nature of the bonding between **HBO** and the protecting group. With an ester-type linkage (**HBO**-$COCH_2CH_2CH=CH_2$), two HT products were obtained and a small amount of HH (7:86:7), where the major product **98** configuration was *syn* (Chart 8, **97**-**99**). With an acetal linkage (**HBO**-$CH_2OCH_2CH=CH_2$), the selectivity was inversed with a HH-type compound as the major product **101** (87%). Additionally, 1,7-hydrogen atom transfer (1,7-HAT) occurred, giving **102** presenting an α-C-C bond product in low yield (4%) (Chart 8, structures **100**-**102**). After cleavage of the ester or acetal bonds, trifunctionalized cyclobutanes could be generated. New assays were performed with a disubstituted alkene (**HBO**-$COCH_2CH_2CH=CHCH_2OH$ and **HBO**-$CH_2OCH_2CH=CHCH_2OH$) to obtain tetrafunctionalized products. With the ester compound, cyclobutane products were isolated even if the global yield was moderate (64%) with a poor selectivity (Chart 8, structures **103** and **104**). Additionally, a bis-lactone has been formed, coming also from 1,7-HAT (Chart 8, structure **105**). In the case of the acetal derivative, although the conversion was total, no significant identification of products could be extracted from the complex mixture obtained after irradiation. The hypothesis proposed by the authors was that numerous 1,5- and 1,7-HAT took place and led to this complex mixture.

For all the other products described in this study, structures were elucidated using NMR analysis. Noticeably, a computational study was carried out to "rationalize the origin of the different observed regioselectivities".

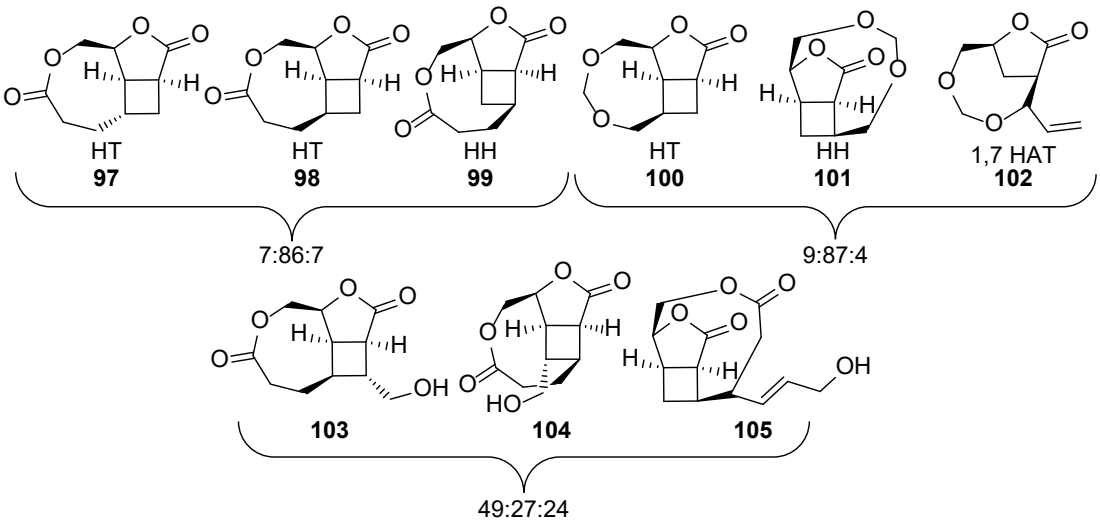


Chart 8. Products of intramolecular [2+2] photoadditions.

It is important to precise that intramolecular photochemical [2+2] cycloaddition has been previously used in the synthesis of stoechospermol by Tanaka et al.[74,83]

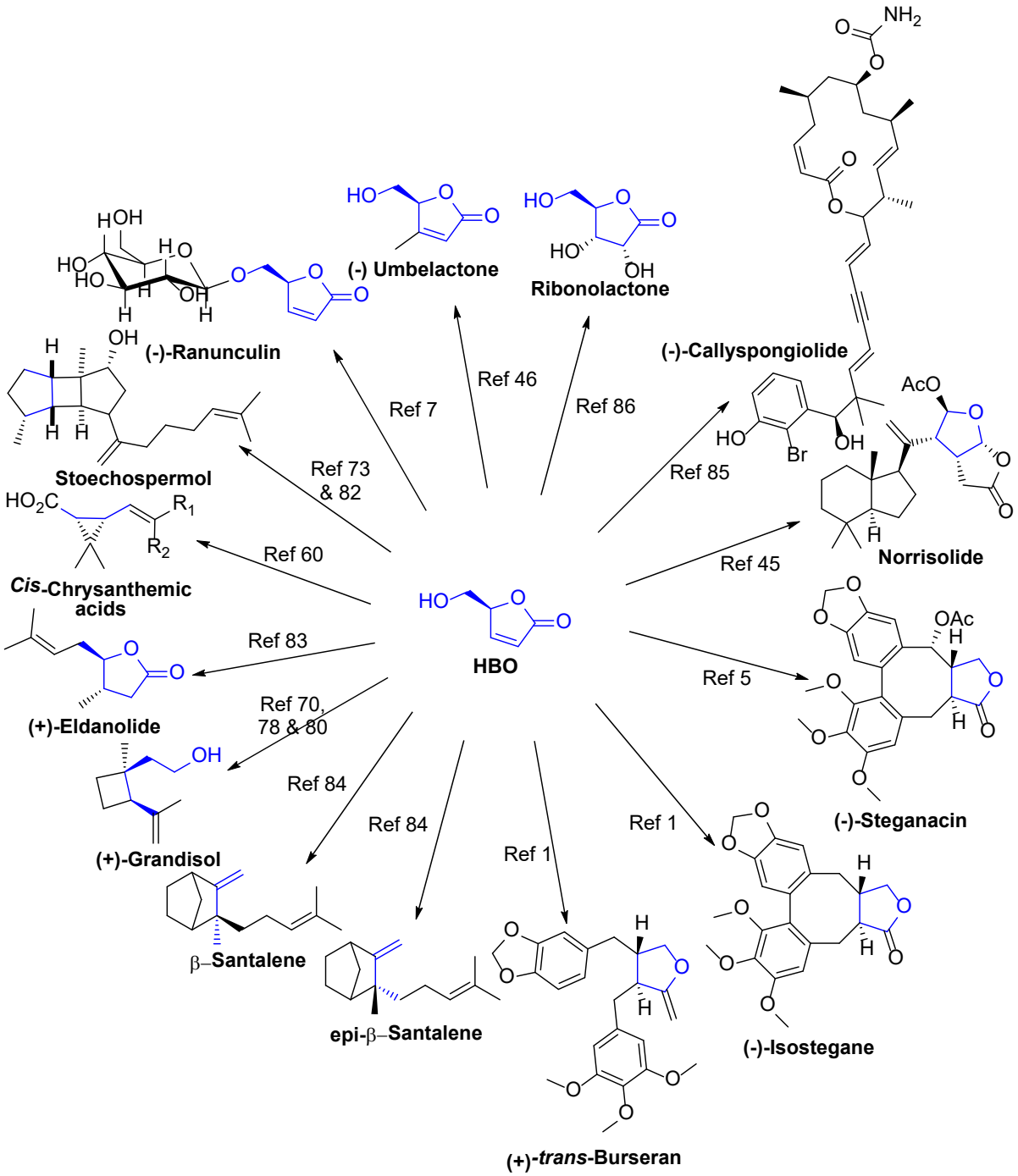
The use of photochemistry to efficiently access particular configurations and/or complex molecules starting from biobased **HBO** can be likened to doubly green chemistry since light is regarded as a clean and traceless reagent.

3. **HBO** DERIVATIVES AS SYNTHONS FOR ORGANIC SYNTHESIS

3.1 Precursor of natural molecules

HBO was used in the syntheses of a wide range of naturally occurring compounds. Due to the presence of a stereogenic center, one of the first use of **HBO** dealt with the total synthesis of enantiopure natural metabolites[5,25,47,84] in order to determine their absolute configuration. For example, umbelactone enantiomers have been selectively synthesized from (*S*)- and (*R*)-γ-

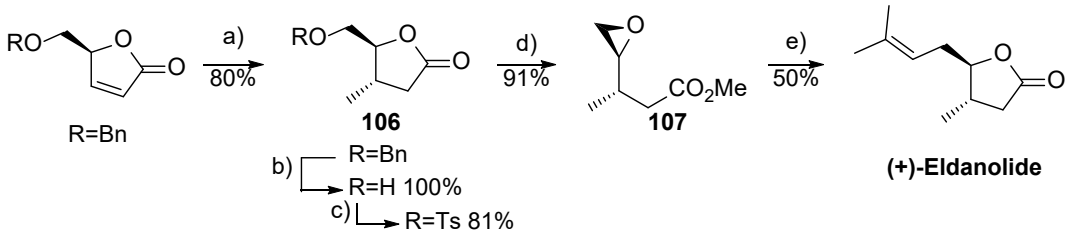
hydroxymethyl-α,β-butenolides in two steps, allowing to determine, by comparison of their optical rotations, the absolute configuration of the natural product, proven as (+)-(*R*)-umbelactone (Scheme 19).[47] The simplest natural product synthesized from **HBO** was its β-glucoside derivative, named (-)-ranunculin in only two steps: coupling of **HBO** and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide using Ag_2O as an activator, followed by complete deprotection (84% overall yield).[7]



Scheme 19. HBO, a precursor for natural molecules.

Among the natural molecules accessible from **HBO**, several belong to the pheromones family isolated from insects and that could be used in bio-control such as eldanolide[84] or (+)-grandisol.[71,79,81] As a common feature in approaches to these two molecules, the first step

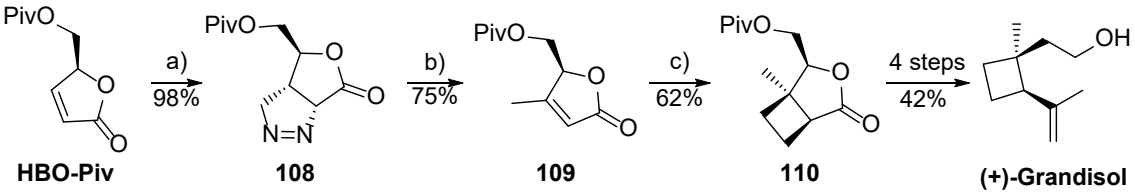
involves the β-methylation of the double bond using two methods, one using lithium dimethylcuprate when the other relies on the thermolysis of pyrazolidine obtained after 1,3-dipolar addition of diazomethane. For eldanolide synthesis, the strategy involved an epoxide formation before the addition of another cuprate derivative (Scheme 20).



a) $(Me)_2CuLi$, Et_2O, -35 °C, b) H_2, Pd/C, AcOEt/EtOH, c) TsCl, Pyridine, d) K_2CO_3, MeOH e) $(\text{vinyl})_2CuLi$, Et_2O, -50 °C

Scheme 20. Synthesis of (+)-eldanolide.

For the synthesis of (+)-grandisol, the key step was the [2+2] cycloaddition reaction with ethylene (Scheme 21).



a) $CH_2N_2.Et_2O$, THF, r.t., dark, 48 h, b) 1,4-dioxane, reflux, 51 h, c) ethylene, h^{ν}, Et_2O, -20 °C, 7 h

Scheme 21. Synthesis of (+)-grandisol.

In the field of crops treatment, cyclopropanic structures belonging to pyrethrin insecticide family have been stimulating targets. In this context, *cis*-chrysantemic acids were synthesized by Mann and Weymouth-Wilson (Scheme 19).[61] The photoaddition of isopropanol to **HBO** (94%) was chosen as the first step for this procedure, yielding an isopropylcyclopropane bicyclic intermediate.

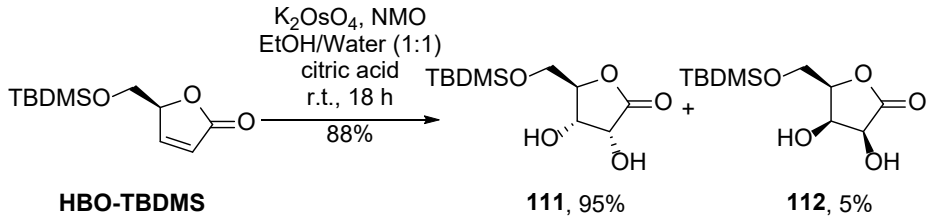
Two multi-step synthesis (25 and 20 steps) were achieved by Tanaka and co-workers to obtain (+)-stoechospermol,[74,83] a polycyclic compound isolated from brown seaweed (Scheme 19). Intramolecular [2+2] photocycloaddition offered an access to the needed tricyclo[5.3.0.0]decane skeleton ring system.

Constituents of East Indian sandalwood oil, β-santalene and *epi*-β-santalene (Scheme 19) were obtained from **HBO** in 4 and 5 steps (38.8 and 27.6% yield respectively), exploring a Diels-Alder reaction with cyclopentadiene as the key step.[85]

In the therapeutic field, Tomioka and co-workers focused their efforts towards the synthesis of three antileukemic lignans, (+)-*trans*-burseran,[1] (-)-isostegane[1] and (-)-steganacin.[5] As previously discussed, the Michael addition was selected as the key pathway to these molecules. More recently, in 2005, Brady et al. have developed a strategy to obtain norrisolide.[46] This toxic and antifeedant substance, produced by sea slugs to protect themselves against predators, was also expected to possess various other interesting biological activities. Indeed, different molecules belonging to this family have shown antifungal, antimicrobial, antiviral and antitumoral properties. The Diels-Alder addition of butadiene to **HBO-TBDPS** was the first of the sixteen steps needed to achieve the total synthesis of norrisolide (7.9% overall yield). Very recently, another high therapeutically potential marine structure, (-)-callyspongiolide, was synthesized. The pathway chosen by Manoni et al. started from **HBO** and involved 14 steps.[86] Because (-)-callyspongiolide is a cytotoxin able to set off cell death by non apoptotic mechanism, it opens a research field for new therapeutic strategies to treat cancer.

Moreaux et al. have published recently a procedure for *syn*-dihydroxylation of protected **HBO** in order to obtain D-ribonolactone derivatives.[87] Puzzingly, D-ribonolactone that had been used as a precursor for **HBO**, became a valuable objective from this same **HBO**. Indeed, since **HBO**

can be synthesized from **LGO** by simpler and greener pathways, it becomes a better starting material. A modified-Upjohn procedure performed on **HBO-TBDMS** (Scheme 22) led to the best yield and stereoselectivity (88% yield and 95:5 diastereomeric ratio). Subsequent TBDMS deprotection with Montmorillonite K10 in a mixture of methanol and water gave D-(+)-ribono-1,4-lactone in 77% yield. D-Ribonolactone has been chosen as a useful intermediate to produce 4-deazaformycin B[88] or (+)-varitriol[89] (respectively antibiotic and antitumoral agents).



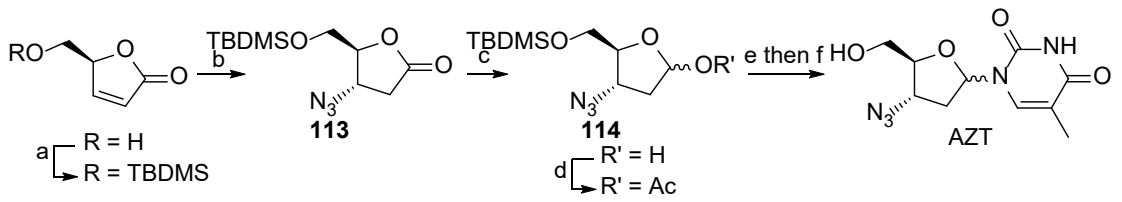
Scheme 22. Dihydroxylation of **HBO-TBDMS** under modified Upjohn conditions.

HBO has also been used as the starting material for deoxyribose analogues production.

3.2 Nucleosides derivatives starting from **HBO**

The nucleosides analogues produced from **HBO** were mainly meant to treat human immunodeficiency virus (HIV).

Chu et al. have synthesized the well-known antiviral AZT[27] using Michael addition of an azide anion to **HBO-TBDMS**, before the controlled reduction of lactone to lactol with diisobutyl aluminum hydride. The lactol, **114**, was then acetylated to promote the condensation with silylated thymine. AZT was finally obtained after desilylation (Scheme 23). The same method has been used for preparation of α- and β-nucleosides derivatives of uridine (AZDU), purine (**115** and **116**) and inosine (**117**) (Chart 9).[28] Unfortunately, these compounds did not exhibit any inhibition activity towards HIV.



Scheme 23. Synthesis of AZT from **HBO**.

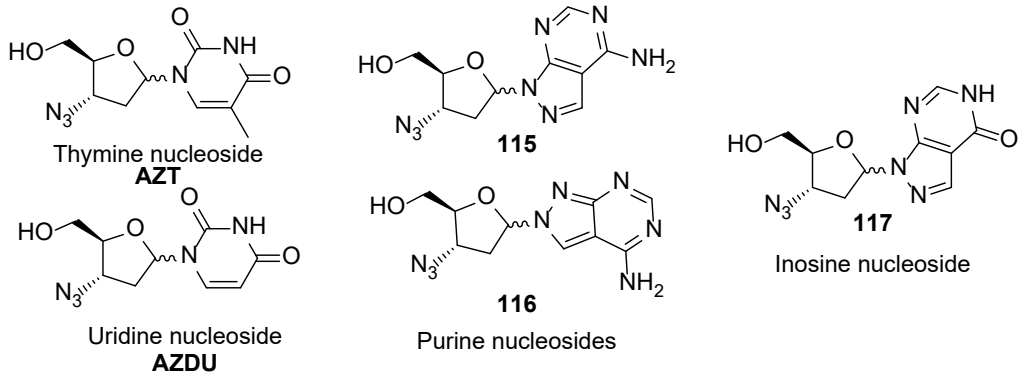


Chart 9. Nucleosides obtained from various bases.

Mann et al. have used the photoaddition methodology as a key step to form (*3'R*)-2',3'-dideoxy-3'-hydroxymethyl-nucleosides **52** (Chart 10).[63] Diverse heteroaromatic bases (cytosin, 5-fluorocytosin, uracil, 5-chlorouracil and thymin) have been used to create a library of targets. Compounds emerging from this library were screened for antiviral activity against six viruses (HSV-1 and HSV-2 herpes simplex virus, VZV varicella zoster virus, HCMV human cytomegalovirus, HIV-1 and influenza). The (*3'R*)-2',3'-dideoxy-3'-hydroxymethyl-nucleoside of cytosin has shown activity against all these viruses, except for influenza, with IC_{50} values varying between 20 and 1.2 μmol.L^{-1} for varicella zoster virus (VZV) and HIV, respectively. The chloro-cytosin adduct was less efficient and other ones did not demonstrate any activity. A fluoromethyl compound, **119**, has also been synthesized and primary result against HIV was encouraging (Chart 10). The same team has investigated synthetic routes to obtain 2',3'-dideoxy-

3'-hydroxymethyl-4'-thionucleosides **120** (Chart 10).[64] The initially chosen pathway starting from **HBO** was not efficient, so a longer route has been selected starting from diethyl (*S,S*)-tartrate. Unfortunately, the tested thionucleosides did not exhibit any activity.

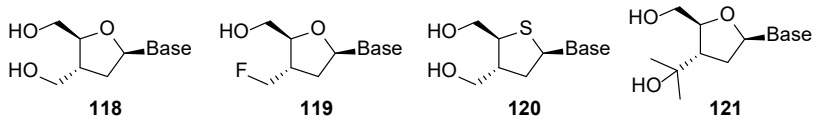


Chart 10. Nucleosides and thionucleosides synthesized by Mann et al. (**118**-**120**) and Wengel et al. (**121**).

Always using the great potential of photochemistry, Wengel and co-workers have found an access to 3'-*C*-branched 2',3'-dideoxynucleosides **121** (Chart 10).[66] Addition of isopropanol or cyclopentanol directly on **HBO** could be performed under irradiation in the presence of benzophenone. Then, the pathway to obtain nucleosides appears similar to those described previously. Additionally, they have described the free radical deoxygenation of the photoadduct *via* a transformation into methoxalyl esters followed by treatment with tri-*n*-butyltin hydride. The original lactones were obtained in good yields (72 and 83% from isopropyl and cyclopentyl-adducts, respectively) and were anticipated as new substrates to enlarge their nucleoside library.

Alibès and co-workers[78] have used cyclobutane derivatives to form cyclobutane-fused nucleosides with different bases such as thymin, adenin or 6-chloropurin. In a subsequent work, Flores et al.[77] have observed a moderate activity against HIV for the cyclobutane-**HBO**-adenin compound, **122** (Chart 11). As previously mentioned, they have also synthesized chloro and fluoro analogues. Over the fifteen synthesized halogenated nucleosides, only one exhibited a moderate activity, namely the α-chloro-cyclobutane-**HBO**-β-adenin, **123** (Chart 11). Their conclusion was that the introduction of a fused cyclobutane decreased the affinity with the cellular kinases or the reverse transcriptase, making them consequently poor substrates. Diaz-

Rodriguez et al. have used a Diels-Alder cycloaddition to access similar conformationally constrained bicyclic nucleosides.[43] **HBO** was protected with a TBDPS group to ensure the total selectivity for the addition of butadiene. Then, as observed for other syntheses of nucleosides, the lactone could be reduced to a lactol, which was further acetylated and substituted by pyrimidic or puric bases. The authors have achieved a library of 25 compounds which were then tested against HIV-1. Six compounds have delightly express activity, and among them, the inosin analogue, **124**, seemed the most potent (Chart 11). Additionally, several functionalizations of the purin ring have slightly reduced the antiviral activity, and drastically the cytotoxicity for blood mononuclear cells.

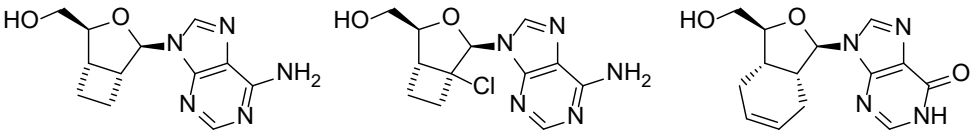


Chart 11. Bicyclic nucleosides analogs exhibiting anti-HIV activity.

Finally, Kushida et al.[90] have used **HBO** to synthesize not just a single nucleoside unit but a DNA model structure. This model allowed evaluating the carcinogen potential of ptaquiloside (Chart 12). This intriguing molecule isolated from bracken fern, is supposed to be responsible for intestinal and bladder carcinomas in animals.

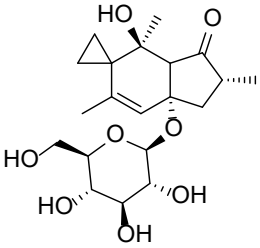


Chart 12. Structure of Ptaquiloside.

HBO has also been used to synthesize other complex molecules than nucleosides to investigate alternative treatments for various diseases.

3.3 Therapeutically promising products derived from **HBO**

To the best of our knowledge, the first attempt to synthesize a therapeutic agent starting from **HBO** is the preliminary work of Magnus and Becker in 1987.[8] In 10 steps with a 7.5% overall yield, they have completed the synthesis of 6a-carbocycline (Chart 13), a more stable analog of prostacyclin (Chart 13), a valuable compound used as a vasodilatator and to prevent platelet plug. Santiago de Alvarenga and Mann, on their side, have synthesized analogues **56** and **57** (Chart 5) of lindelofidine (Chart 13), an alkaloid, using a photoaddition of pyrrolidine to butenolides.[70]

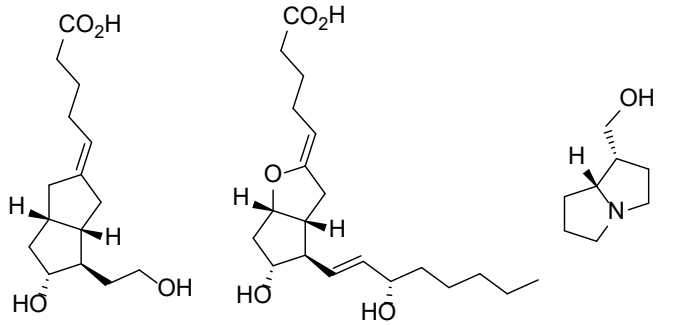
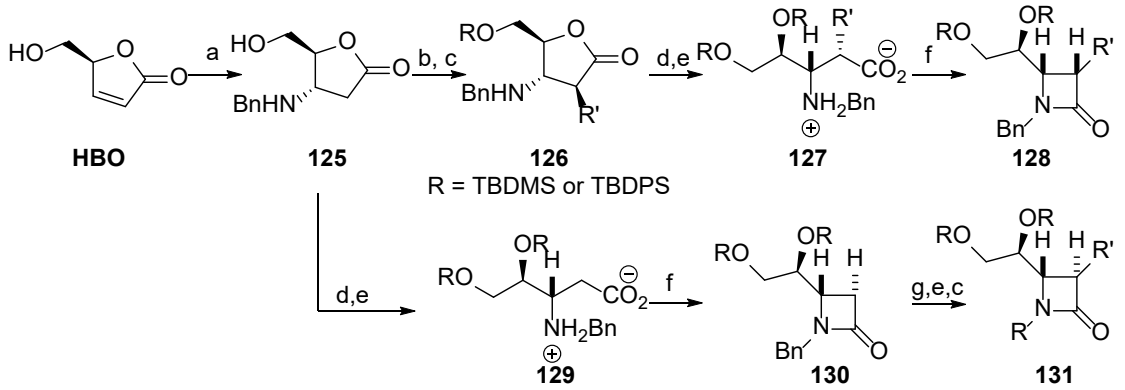


Chart 13. Structures of 6a-carbocyclin, prostacyclin and lindelofidine.

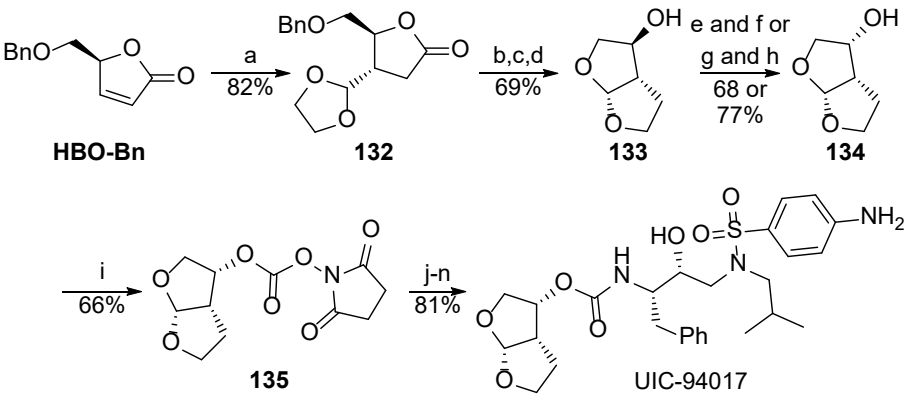
Discovery of new antibiotics is an important target to face the increased resistance of bacteria. Collis et al. have reported the synthesis of an aminolactone pattern that can be used as a valuable precursor for azetidinones, a motif displayed in many antibiotics.[30] Aza-Michael addition of benzylamine to **HBO** provided the 3-substituted product **125**, which can be further alkylated on position 2, giving **126**. Opening of the resulting lactone under basic conditions (with NaOH for example) led to a β-amino acid, **127**. After a protecting step, this compound can be closed to give

cis-3,4-azetidinones of type **128**. The *trans*-isomer, **131** has been observed if the alkylation is performed after ring closure (Scheme 24).



Scheme 24. Synthesis of *cis*- and *trans*-azetidinones from **HBO**.

As described in the paragraph dedicated to nucleosides synthesis, fighting against HIV remains a constant work. To that purpose, Ghosh et al. have developed bis-tetrahydrofuranyl ligands to inhibit HIV protease.[68,69] These bis-tetrahydrofurans have been prepared from various protected-**HBO** derivatives using the photoaddition of 1,3-dioxolane (Table 4), prior to deprotection and reduction with lithium aluminum hydride, followed by a cyclization mediated by a catalytic amount of hydrochloric acid. The chirality at the hydroxyl-position can be inversed through oxidation/reduction procedure (68%) or using a Mitsunobu reaction followed by deprotection (77%). Finally, after esterification of the hydroxyl moiety with disucinnimidyl-carbonate, five steps were required to achieve the synthesis of UIC-94017, a ligand that inhibits HIV protease (Scheme 25).



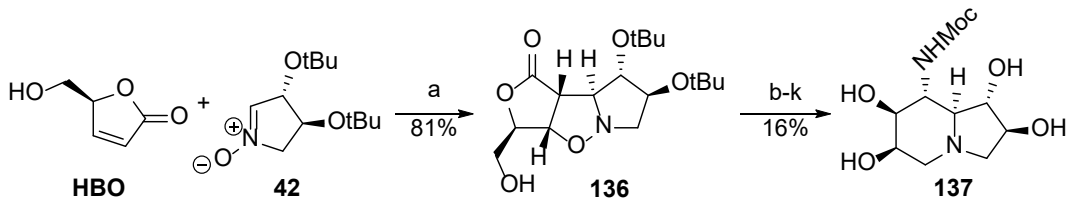
a) h^{ν}, benzophenone (10-15 mol%), [1,3]-dioxolane, b) H_2, Pd/C, MeOH, c) LAH, THF, d) 1 N HCl, THF/H_2O, e) TPAP, NMO, f) $NaBH_4$, EtOH, g) *p*-$NO_2C_6H_4CO_2H$, Ph_3P, DIAD, h) aq. LiOH, i) Disuccinimidyl-carbonate, Et_3N, CH_2Cl_2, j) 2-propanol, 84 °C, k) *p*-$NO_2C_6H_4CO_2H$, aq. $NaHCO_3$, CH_2Cl_2, l) H_2, Pd/C, m) CF_3CO_2H, CH_2Cl_2, n) Et_3N, CH_2Cl_2.

Scheme 25. Synthesis of an inhibitor of HIV-protease from **HBO-Bn**.

Other molecules have been synthesized from **HBO** in the hope to find new enzyme inhibitors.

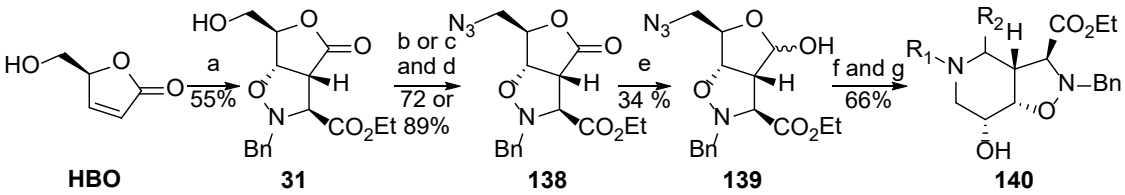
In their study dedicated to the evaluation of a library of γ-butyrolactones towards bacterial protein binding, Kunzmann et al. have used **HBO** as a useful starting material.[91] They have declared interest in such structures because of their natural abundance. Indeed, according to them, 10% of all known natural compounds contained a γ-butyrolactone moiety. Their results indicated that the binding of their molecules with proteins was not covalent but reversible. Following the same idea, Stecko et al. have performed the synthesis of amino-iminosugar - another widespread pattern in nature - evaluated for its ability to inhibit a panel of standard glycosidases.[92] In order to build their 8-amino-indolizidines, they have chosen **HBO** as the starting material in 1,3-dipolar cycloadditions to form the key synthetic intermediate **136** (Scheme 26). Unfortunately, they did not highlight any inhibition activity. More recently, Hoogenboom et al. have synthesized a library of glycomimetic compounds to offer a wide range of structures for comprehensive studies of interaction between enzymes (such as intestinal glucosidases or glycosyl transferases) and these substrates.[93] They have added nitrones on **HBO**

as the first step. Subsequently, the hydroxyl group was substituted with an azide after mesylation, followed by controlled lactone reduction into lactol. Finally, a ring rearrangement occurred to achieve the access to glycomimetic building blocks (Scheme 27).



a) Toluene, r.t. then reflux, b) NH_3, MeOH, r.t., c) TBDPSCl, Imidazole, CH_2Cl_2, -15 °C then r.t., d) $PhI(OAc)_2$, MeOH, r.t., e) TBAF, THF, r.t., f) MsCl, EtN_3, CH_2Cl_2, -15 °C then r.t., g) H_2, Pd/C, AcOEt/MeOH (4:1) r.t., h) Ac_2O, EtN_3, 0 °C then r.t., i) CF_3Co_2H, r.t., j) Ac_2O, Et_3N, 0 °C then r.t., k) 1% NH_3 in MeOH, r.t.

Scheme 26. Synthesis of 8-amino-indolizidines from **HBO**.

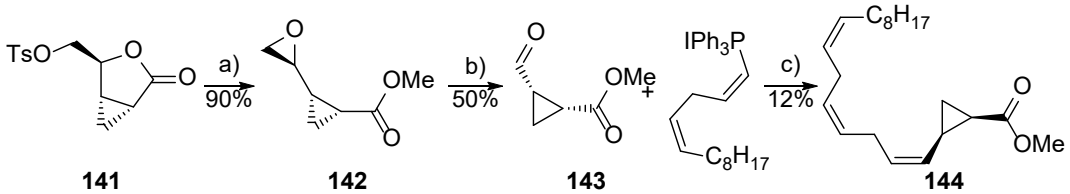


a) Nitrone, toluene, reflux, 4.5 h, b) $(PhO)_2P(O)N_3$, diisopropyl azodicarboxylate, PPh_3, THF, -20 °C then r.t., 1.5 h, d) MsCl, Et_3N, CH_2Cl_2, 0 °C, 50 min, e) NaN_3, DMF, 60 °C, 1.5 h, f) BH_3-SMe_2, THF, 4-20 °C, 7 h, g) $(AcO)_3BHNa$, THF, 4 °C, 1.5 h.

Scheme 27. Synthesis of glycomimetic compounds from **HBO.**

Butler et al. have synthesized methyl (1*R*,2*S*)-2-[1'*Z*,4'*Z*,7'*Z*)-hexadeca-1',4',7'-trienyl]cyclopropanecarboxylate **144**, [48] with the goal to inhibit the 5-lipoxygenase, an enzyme at the origin of a cascade reaction involved in inflammatory and allergic diseases. As previously described, the cyclopropane ring has been obtained from **HBO** using 1,3-dipolar addition of diazomethane followed by nitrogen elimination under photoirradiation conditions (Scheme 8). After tosylation, opening of the lactone under basic conditions (MeONa, MeOH) and the concomitant cyclization on the tosylate lead to an epoxide moiety. Oxidative cleavage of this

epoxide **142** released an aldehyde **143**, which was then subjected to a Wittig olefination to afford the desired product (Scheme 28).

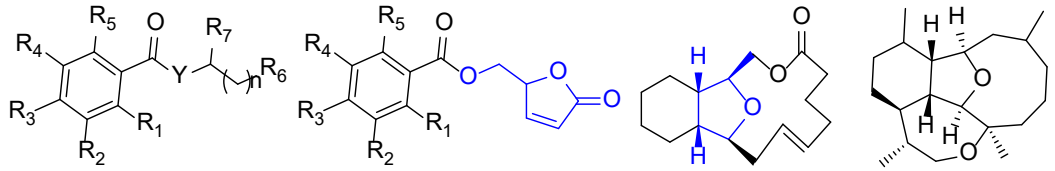


141 **142** **143** **144**

a) MeONa, MeOH, b) HIO_4, 1,4-dioxane/ether (1:1), c) *n*-BuLi, THF

Scheme 28. Synthesis of methyl (1*R*,2*S*)-2-[1'*Z*,4'*Z*,7'*Z*)-hexadeca-1',4',7'-trienyl]cyclopropanecarboxylate.

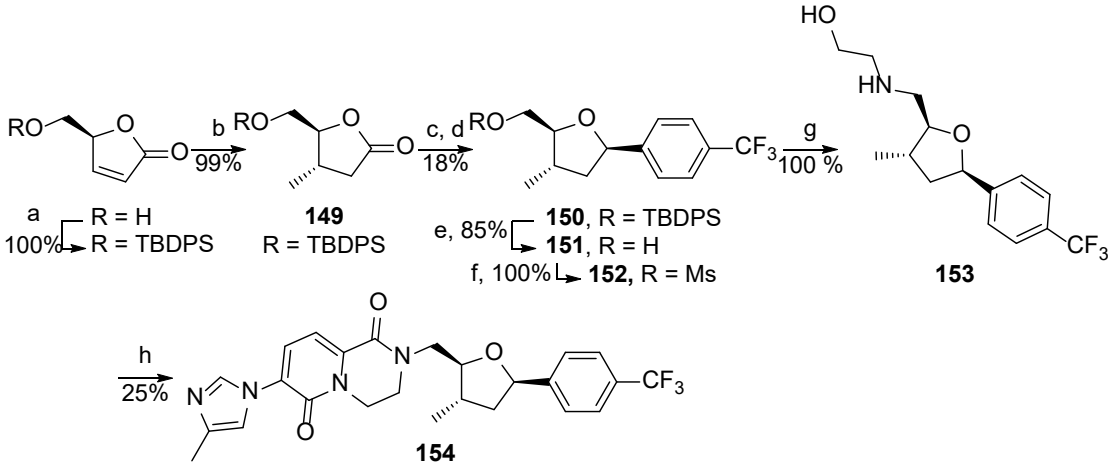
In 2002, Kastelic et al. have claimed the access to a family of benzoic acid derivatives, able to inhibit the formation of cytokines, a category of peptides involved in cellular signaling.[94] Their overexpression is invoked in various disorders such as arthritis, psoriasis and Crohn's disease. Although the general formula **145** included numerous compounds, their examples always represented **HBO** - or its enantiomer - esterified by benzoic acid derivatives **146** (Chart 14). They have also suggested that their molecules could be applied for cancer prophylaxis or treatment. Noticeably, the same hope was formulated by Welford et al.[45] They have synthesized a library of 2,11-cembranoïd analogs and tested them on cancer cell lines. Even if these molecules did not demonstrate any cytotoxicity, they were able to drastically reduce their migrations. Interestingly, a less complex structure, such as **147**, provided similar activity compared to the natural molecule **148** (Chart 14).



145 **146** **147** **148**

Chart 14. General structures of molecules claimed by Kastelic et al. **145** and an example of synthesized structure **146**. Structure **147** obtained by Welford *versus* natural 2,11-cembranoïd **148**.

The work of Am Ende et al., dedicated to the modulation of enzymatic activities, targeted neurodegenerative or neurological diseases such as Alzheimer and Down syndrome.[95] They have designed a set of bicyclic pyridinones that could increase the γ-secretase complex activity, in order to limit the aggregate formation of amyloid β-proteins responsible of the neuronal disorder. **HBO** has been used as the precursor in the synthesis of the eastern part of this bicyclic pyridinone. In the presented example, all the functionalities of **HBO** were involved to build the desired product (Scheme 29).



a) TBDPSCl, imidazole, DMF, r.t., 18 h, b) CuBrMe2S, CH3Li, Et2O, 0 °C then -20 °C, 0.5 h, c) CeCl3, [4-(Trifluoromethyl)phenyl]magnesium bromide, THF, -40 °C, 1 h, d) Et3SiH, BF3.Et2O, -78 °C, 1 h e) TBAF, THF, r.t., 1 h, f) Et3N, CH2Cl2, MsCl, 0 °C, 45 min, g) 2-aminoethanol, 85 °C, 2h, h) 5-(4-Methyl-1/-/-imidazol-1-vl)-6-oxo-1.6-dihvdropyridine-2-carboxvlic acid, hydrochloride salt, A/,/V-diisopropylethylamine, HATU, CH2Cl2, reflux, 2h.

Scheme 29. Synthesis from **HBO** of a bicyclic pyridinone designed by Am Ende et al.[91].

Chen et al. have also used an agonist approach to propose new prophylaxis and treatment of hepatitis B and C viruses (HBV or HCV).[96] They have synthesized prodrugs able to link to the

Toll-like receptor 7, a structure involved in the detection of invading pathogens and then initiating innate immune responses. Over the molecules of general formula **155**, compounds such as **156** could be synthesized from **HBO** (Chart 15).

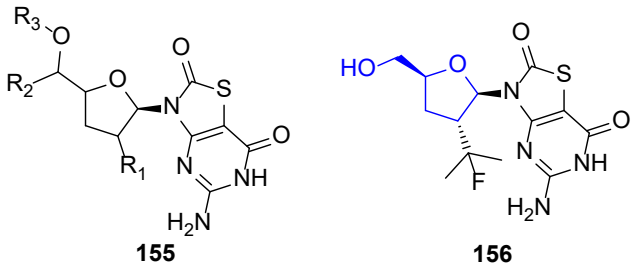
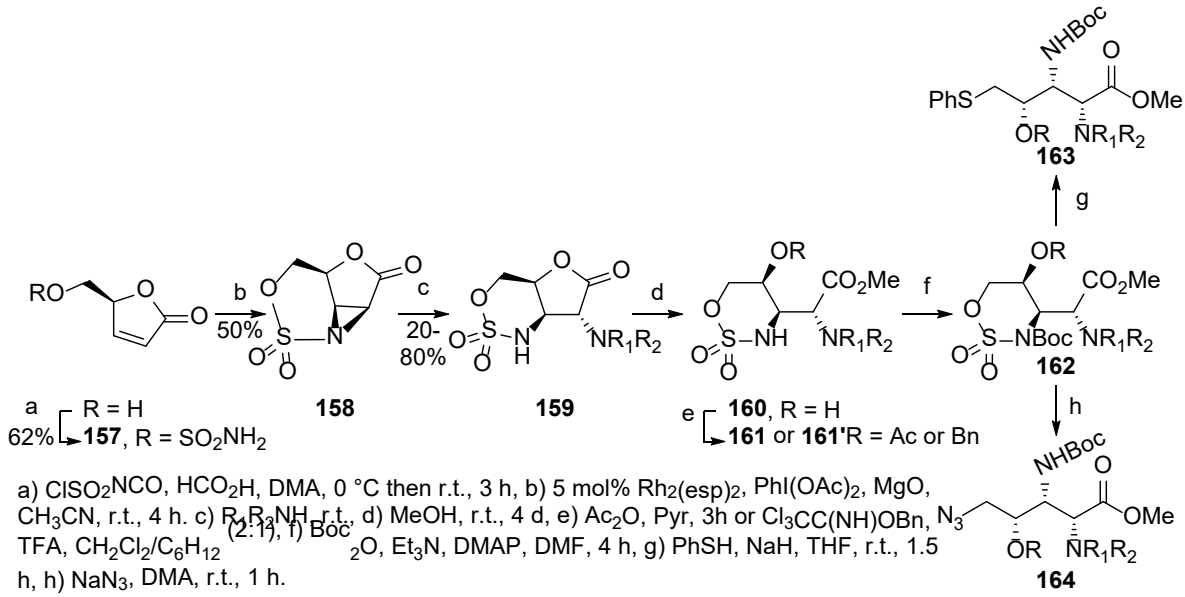


Chart 15. General formula of compounds **155** designed by Chen et al.[92] and one synthesized from **HBO** (**156**).

The use of **HBO** is not only limited to natural or pharmaceutical products even those one are involved in the major applications.

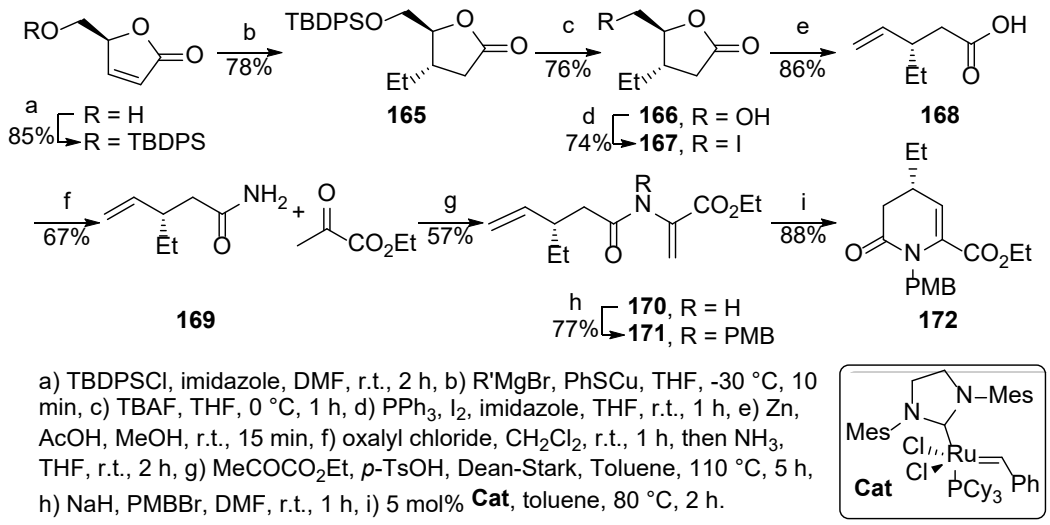
3.4 Other applications of **HBO**.

The presence of a stereogenic center on **HBO** is a great asset. It can be used to assess the selectivity of chemical pathways,[9] to synthesize optically active molecules[32,97] or new α,β-diamino acid derivatives.[98] This last work from Siqueira Valle et al. described an intramolecular reaction catalyzed by a rhodium complex. **HBO** was submitted to chlorosulfonylisocyanate to give the corresponding 5-*O*-sulfamate which then underwent a rhodium-catalyzed intramolecular aziridination. The aziridino-γ-lactone was subsequently opened with primary or secondary amines on C2-position with an *anti* selectivity. To achieve the approach to α,β-amino acids, the lactone could be opened with methanol for instance, followed by acetylation or benzylation of the released hydroxyl group, to avoid any relactonization process. The amine moiety was then protected with a Boc group, followed by a treatment with sodium azide or phenylthiolate, leading to the opening of sulfamate ring with concomitant loss of SO_3 (Scheme 30).



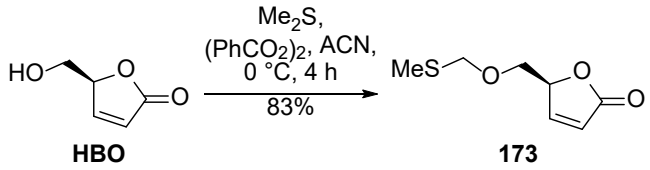
Scheme 30. Synthesis of α,β-diamino esters starting from **HBO**.

HBO can also act as a precursor for the elaboration of other heterocyclic compounds *via* metal catalysis. Van den Broek and co-workers have suggested the synthesis of nitrogen heterocycles involving a ring closing metathesis (RCM) catalyzed by a ruthenium complex.[97] **HBO** could be transformed in 6 steps into unsaturated amides with a global yield varying between 18 and 21%. These unsaturated amides were condensed with ethyl pyruvate to provide compounds of general formula **170** that were subjected to RCM and led to 2-oxopiperidine carboxylic esters **172** (Scheme 31), a pattern found in numerous natural molecules.



Scheme 31. Synthesis of optically active 2-oxopiperidine carboxylic acids starting from **HBO**.

Recent work by Sharipov et al.[99] demonstrated that **HBO** can be efficiently converted into methylsulfanyl-**HBO**, **173** (Scheme 32). This molecule exhibits high fungicidal activity against *Bipolaris Sorokiniana*, a crop parasite.



Scheme 32. Methylsulfanylation of **HBO**.

Due to the very recent new synthetic pathway to **HBO**,[3] a first attempt of polymerization emerged, performed by Diot-Neant et al.,[100] reporting the free radical polymerization of **HBO** derivatives. They have achieved the enzymatic synthesis of methacrylated **HBO**, 1**74** (64% yield), by reaction of methyl methacrylate and **HBO** in the presence of *Candida antarctica lipase B* (CAL-B). They have also performed the chemical methacrylation with methacrylic anhydride and triethylamine used as a base. This method led to dehydrated **HBO**, the so-called 5-methylene-2(*5H*)-furanone **175**. Free radical homopolymerization of methacrylated **HBO** was

attempted with AIBN as a promoter, but only insoluble oligomers have been observed. The authors have finally succeeded in obtaining polymers from the hydrogenated derivative of **HBO**, **2H-HBO** (Chart 16).

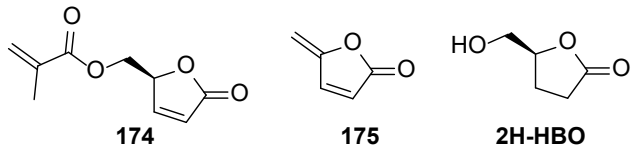


Chart 16. Methacrylated **HBO**, **174**, 5-methylene-2(*5H*)-furanone, **175** and **2H-HBO.**

Noticeably, **2H-HBO** is readily accessible in excellent yield (90%) from **HBO** using palladium-catalyzed hydrogenation[19] or OYE 2.6 (old yellow enzyme 2.6)-catalyzed hydrogen- and solvent-free reduction.[101] This reagent is also a valuable synthon for organic chemists with more than hundred and forty literature references using it as starting material.

CONCLUSION

Although **HBO** has been known for more than 40 years, industrially relevant synthetic processes allowing its large-scale production were only reported recently. Nevertheless, it did not prevent chemists from investigating the potential of this multifunctional chiral molecule. In particular, there were many studies dealing with the reactivity of the polarized double bond and the influence of the chirality of **HBO** on Michael addition, Diels-Alder reaction, 1,3-dipolar cycloaddition or in photochemistry. Besides these fundamental studies, **HBO** was also used as starting material for total syntheses of various natural or synthetic compounds, more particularly for therapeutic applications.

The recently published and patented sustainable, industrially and economically relevant synthetic access to **HBO** thus opens the way to the potential industrialization of these synthetic

pathways that remained at the fundamental stage yet due to, not only the high price of **HBO**, but also its limited availability.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

ACKNOWLEDGMENT

The authors are grateful to Grand Reims, Département de la Marne, and Grand Est for financial support.

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