Total synthesis of (–)-herbaric acid through organocatalyzed asymmetric halolactonization of acrylate-type benzoic acids

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Abstract: The total synthesis of (–)-herbaric acid has been achieved through the stereoselective synthesis of 3-substituted isobenzofuranones with a new organocatalytic route. When combined with a catalytic amount of benzoic acid, quinidine thiocarbamates based bifunctional catalysts have demonstrated their efficiency for the distereoselective halolactonization reaction of acrylate-type benzoic acids bearing a chiral alkoxycarbonyl group on the carbon-carbon double bond. High diastereomeric excesses were obtained thanks to a positive match effect between the (+)-menthyl ester group and the chiral organocatalyst.

Keywords: *Asymmetric organocatalysis, Cinchona alkaloids, halolactonization reaction, 3-substituted isobenzofuranones, herbaric acid*

Introduction

The 1(3*H*)-isobenzofuranone moiety, also called phthalide, is one of Nature's most popular structural motif and this ring system lies at the heart of a rich and diverse group of natural products [1]. Phthalides that contain a C3-substituent represent a smaller subset of this class which exhibits a wide range of biological activities [2]. Representative examples include typhaphtalide [3], 3-butylphthalide [4], and alcyopterosin E [5] (Figure 1). In addition, they constitute the main core of a minor group of natural products such as isoochracinic acid [6] or the fungal metabolite (–)-herbaric acid [7] bearing a carboxymethyl group at the 3 position of the lactone ring system (Figure 1). Consequently, the structural originality of these functionalized chiral isobenzofuranones makes them challenging synthetic targets, and the development of stereoselective methodologies for their synthesis constitutes an area of current interest.

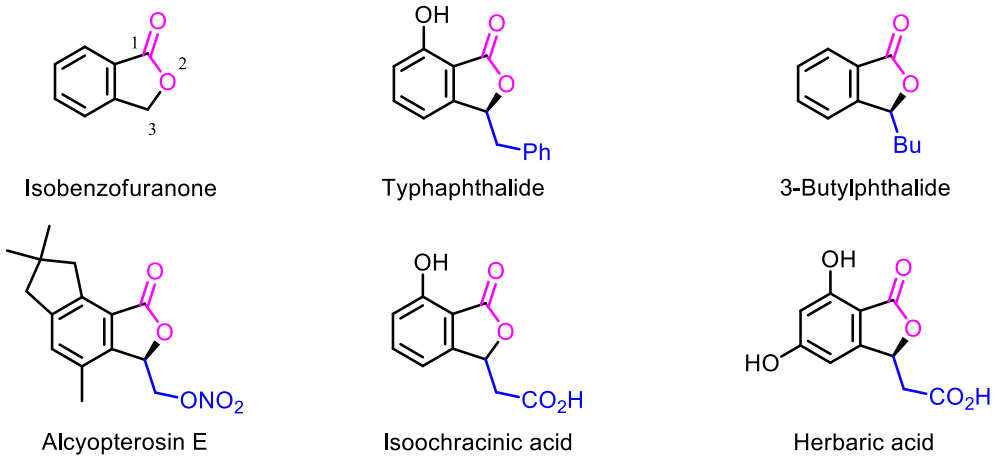


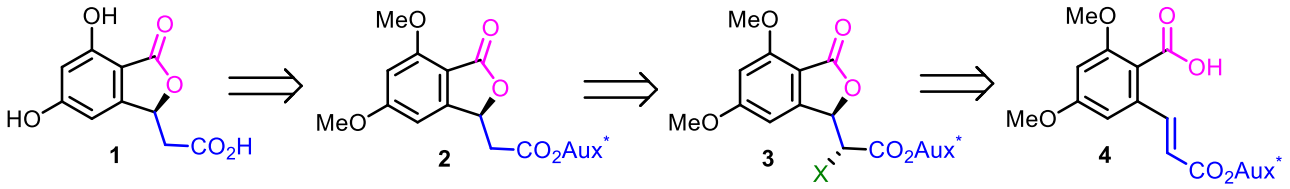
Figure 1. Bioactive natural 3-substituted isobenzofuranones

Organic chemists have a variety of synthetic strategies at their disposal for the racemic synthesis of 3-carboxymethyl isobenzofuranone mainly based upon the lactone ring construction [8]. Paradoxically, only a few efforts have been devoted to the asymmetric synthesis of such functionalized oxygenated heterocycles [9]. Otherwise, starting from racemic 3-substitued phthalides, the synthesis of enantioenriched 3,3-disubstituted benzofuranones has been reported using organocatalyzed reactions like Mannich, allylic alkylation or Michael additions [10]. Since considerable efforts have focused in our laboratory on auxiliary- or catalyst-controlled [11,12] syntheses of enantioenriched isoindolinones, we recently extended our studies to their oxygenated analogues (i.e. isobenzofuranones).

Halolactonization reactions between substrates bearing a carbon-carbon double bond and a carboxylate nucleophile are powerful transformations in organic chemistry. If extensive efforts have been recently devoted to the development of stereoselective versions under reagent or catalyst control [13], the range of studied substrates is still limited because only alkyl- and aryl-substituted pentenoic or hexenoic acid derivatives were examined in most cases. Hence, despite a huge synthetic potential, enantioselective halolactonizations of unsaturated benzoic acids has not elicited great synthetic efforts from the scientific community and remained poorly explored [13k,t,x,y]. In this context, we have recently developed a highly regio- and diastereoselective route to enantioenriched brominated isobenzofuranones based upon the first organocatalyzed enantioselective bromolactonization reaction of acrylate-type benzoic acids [14]. Quinidine thiocarbamate based bifunctional catalysts have demonstrated their efficiency when combined with a catalytic amount of benzoic acid and allowed to obtain the targeted bromolactones with promising enantioselectivities (up to 53%). Thus, the application of this efficient methodology to the total synthesis of a representative isobenzofuranone natural product, (–)-herbaric acid, could reasonably be foreseen.

Results and Discussion

From a retrosynthetic point of view, acid **1** could be obtained from the 3-alkoxycarbonylated isobenzofuranone **2** after cleavage of the ester group and deprotection of phenolic methyl ethers. Optically enriched isobenzofuranone **2** could be originated from halolactone **3**, which could be furnished by the organocatalyzed asymmetric halolactonization of benzoic acid **4** bearing an acrylate group at the *ortho* position of the benzene ring. (Scheme 1).



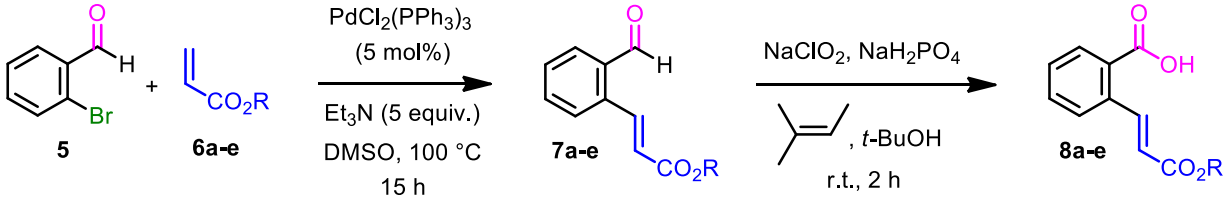
Scheme 1. Retrosynthetic analysis

In order to improve the stereoselectivity of our previously developed enantioselective halolactonization reaction [11], we chose to incorporate a chiral auxiliary in our substrates. Indeed, we anticipated a bulky alcohol issued from the chiral pool would increase the stereoinduction and afford two separable diastereoisomers. Hence, with our synthetic target in mind, our first goal was to identify the best chiral auxiliary and optimize our catalytic system.

1. Synthesis of unsaturated benzoic acids 8a-e

Benzaldehydes **7a-e** were first readily prepared *via* a pallado-catalyzed Heck cross-coupling between 2-bromobenzaldehyde **5** and an array of acrylates **6a-e.** Pinnick oxidation of aldehydes **7a-e** furnished the targeted benzoic acids **8a-e** with good yields (89-97%, Table 1). Having these acrylate-type benzoic acids in hand, the study of their stereoselective halocyclization could be initiated.

Table 1. Compounds **7**, **8** prepared



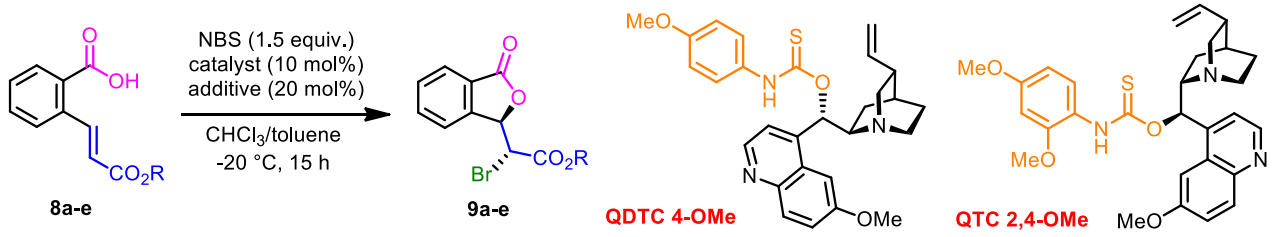
Entry	R	Yield (%)[a]	Yield (%)[a]
1	(+)-Menthyl	**7a** 66	**8a** 97
2	(-)-Menthyl	**7b** 68	**8b** 96
3	(-)-Borneyl	**7c** 59	**8c** 89
4	(+)-Isopinocampheyl	**7d** 64	**8d** 91
9	(+)-Fenchyl	**7e** 60	**8e** 91

[a] Isolated yield

2. Asymmetric intramolecular halolactonization reaction.

Because halolactonization reactions were shown to be performed without the use of any catalyst or additive, control experiments were first investigated. The reaction of **8a** with NBS as halogen source, in toluene at –20 °C led selectively to the brominated isobenzofuranone **9a** *via* a 5-exo-tet cyclization pathway with a good yield (83%) and a modest diastereomeric excess (28% de, Table 2, entry 1). Hence, if the chiral auxiliary could induce some diastereoselectivity, it was too far from the reacting center to have a significant influence on the stereochemical outcome of the reaction (28% de). However, the combination of the optically pure auxiliary and an appropriate chiral organocatalyst allowed a significant increase of the diastereoselectivity. Indeed, when applying bifunctional catalysts developed by Yeung and coworkers [13c] such as catalyst (QDTC 2,4-OMe), we obtained a good conversion and an improved diastereomeric excess (58% de, Table 2, entry 3). While NBS reagent shall be activated by the thiocarbamate unit of the catalyst, the protonated quinidine part may interact with the carboxylate fragment of the substrate, the whole providing a better control of the reaction [13k,r]. Moreover, such increase of the diastereoselectivity was also the result of a good match effect [15] between the chiral ester group and the organocatalyst. Afterwards, we demonstrated the combination of 20 mol% of benzoic acid and QTC 2,4-OMe catalyst led to the desired bromolactone **9a** with the highest diastereomeric excess (76% de, Table 2, entries 4,5). Within these optimized reaction conditions, QDTC 4-OMe and QTC 2,4-OMe catalysts were successfully used in the asymmetric bromolactonization of benzoic acids **8b-e** reaching high yields and modest to good diastereoselectivities (Table 2, entries 6-14). The (+) or (–)-Menthyl group in esters **8a,b** was found to be the best chiral auxiliary (Table 2, entries 5, 6). If one equivalent of catalyst QDTC 4-OMe and two equivalents of benzoic acid additive were used, the diastereomeric excess could be slightly increased (Table 2, entry 7). Finally, performing the reaction at temperatures below –20 °C resulted in lower yields and diastereomeric excesses.

Table 2. Synthesis of bromo isobenzofuranones **9a-e**.

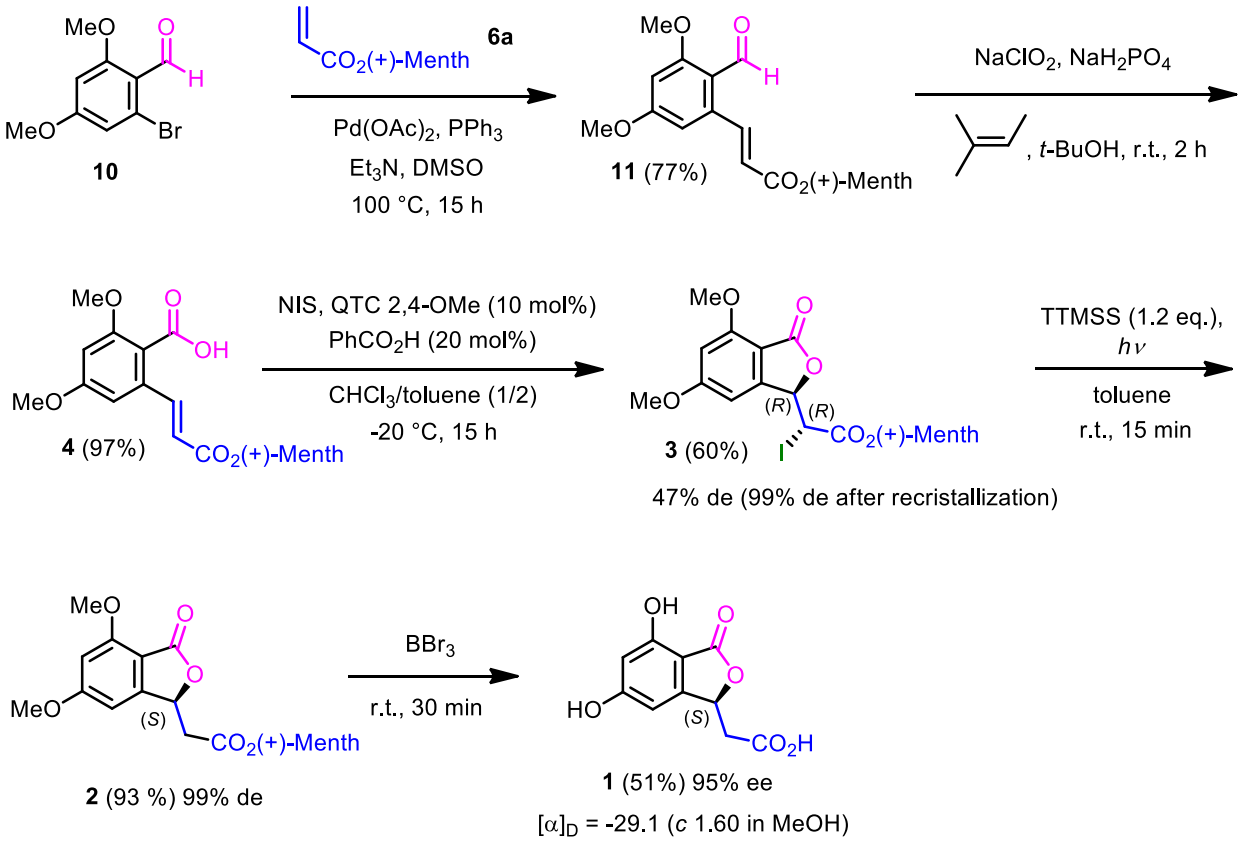


Entry	R	Catalyst	Additive	Yield (%)[a]	D.e. (%)[b]
1	(+)-Menthyl	–	–	**9a** 83	28
2	(+)-Menthyl	QDTC 4-OMe	–	**9a** 85	18
3	(+)-Menthyl	QTC 2,4-OMe	–	**9a** 88	58
4	(+)-Menthyl	QDTC 4-OMe	$PhCO_2H$	**9a** 85	10
5	(+)-Menthyl	QTC 2,4-OMe	$PhCO_2H$	**9a** 83	76
6	(–)-Menthyl	QDTC 4-OMe	$PhCO_2H$	**9b** 82	74
7[c]	(–)-Menthyl	QDTC 4-OMe	$PhCO_2H$	**9b** 85	79
8	(–)-Menthyl	QTC 2,4-OMe	$PhCO_2H$	**9b** 88	32
9	(–)-Borneyl	QDTC 4-OMe	$PhCO_2H$	**9c** 91	45
10	(–)-Borneyl	QTC 2,4-OMe	$PhCO_2H$	**9c** 88	15
11	(+)-Isopinocampheyl	QDTC 4-OMe	$PhCO_2H$	**9d** 93	51
12	(+)-Isopinocampheyl	QTC 2,4-OMe	$PhCO_2H$	**9d** 90	32
13	(+)-Fenchyl	QDTC 4-OMe	$PhCO_2H$	**9e** 93	56
14	(+)-Fenchyl	QTC 2,4-OMe	$PhCO_2H$	**9e** 90	37

[a] Isolated yield from 0.1 mmol reagent at 0.1M. [b] Measured by HPLC. [c] Reaction with 1 equiv. catalyst and 2 equiv. additive.

3. Total synthesis of (–)-herbaric acid.

Next, we turned our attention to the total synthesis of the targeted (–)-herbaric acid. In spite of a simple molecular structure, only one total synthesis of this natural isobenzofuranone has been reported so far. In 2010, Brimble et al. [9a] developed an efficient methodology which allowed access to enantioenriched (–)-herbaric acid (84% ee). In order to create the C3 stereocenter, the synthetic route relied on a microwave assisted chemoenzymatic resolution. According to the previously described procedure, Heck cross-coupling between aryl bromide **10** and (+)-menthyl acrylate **6a** furnished benzaldehyde **11** which was then oxidized with sodium chlorite into the corresponding carboxylic acid **4** (Scheme 2). Unfortunately, organocatalyzed bromolactonization of unsaturated benzoic acid **4** was more difficult than expected mainly due to competitive bromination of the electron rich aryl moiety. Gratifyingly, the use of the less reactive *N*-iodosuccinimide [16] avoided the formation of S_EAr byproducts and led to the targeted iodolactone **3**. The latter was obtained with a satisfactory yield and a 60% diastereomeric excess. On a larger scale, from 0.1-15 mmol, iodolactone **3** was obtained with a 99% de after recrystallization (Scheme 2).



Scheme 2. Total synthesis of (–)-herbaric acid **1**

The stereochemistry (2*R*, 3*R*) of iodoisobenzofuranone **3** was determined by X-ray analysis and confirmed the postulated ester-halogen anti relationship (Figure 2). Radical deiodination of **3** was then performed under irradiation with Tris(trimethylsilyl)silane (TTMSS) [17] in toluene and afforded the isobenzofuranone **2** in high yield and optical purity (Scheme 3). Finally, concomitant cleavage of the (+)-menthyl auxiliary from the ester group and demethylation of aromatic methylethers with boron tribromide [9a] afforded the targeted (–)-herbaric acid **1** without significant loss of enantiopurity (95% ee).

The absolute configuration of the stereogenic center was confirmed to be (*S*) from the sign of the specific rotation of **1**, and the enantiopurity of our synthetic (*S*)-(–)-herbaric acid **1** was clearly established from the optical rotation as well as chromatography and spectroscopy data, $[\alpha]_D$ –29.1 for (3*S*)**-1** (*c* 1.60 in MeOH) (95% ee), $[\alpha]_D$ –27.0 for the natural product (*c* 0.18 in MeOH) [7].

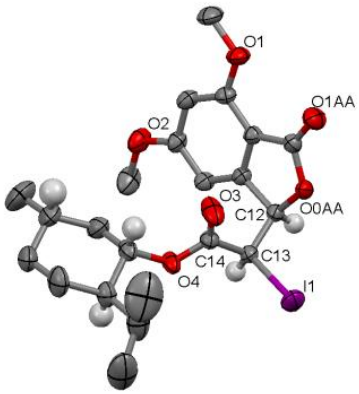


Figure 2. ORTEP plot of (*R*)-iodoisobenzofuranone **3**.

Conclusion

In summary, we have achieved the total synthesis of (–)-herbaric acid by developing an efficient and highly regio- and diastereoselective route to halogenated isobenzofuranones. The key step of our methodology is based upon an organocatalyzed asymmetric halolactonization reaction of acrylate-type benzoic acids bearing a chiral alkoxycarbonyl electron withdrawing group at the carbon-carbon double bond. When combined with a catalytic amount of benzoic acid, quinidine thiocarbamate bifunctional catalysts have demonstrated their efficiency and allowed us to synthesize halolactones with promising diastereoselectivities (up to 76%) thanks to a positive match effect between the (+)-menthyl ester group and the chiral organocatalyst. However, along the total synthesis of the targeted (–)-herbaric acid, such bromolactonization proved to lead also to S_EAr byproducts. The use of NIS overcame that drawback and led to the targeted (2*R*, 3*R*) iodoisobenzofuranone in satisfactory yield and diastereomeric excess, a 99% de being obtained after recrystallization. Further radical deiodination and concomitant cleavage of the (+)-menthyl ester auxiliary and demethylation of aromatic methylethers afforded the targeted (–)-herbaric acid in a high enantiopurity.

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