Tetrahedron 67 (2011) 6859–6867

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Highly regio- and diastereoselective halohydroxylation of olefins: a facile synthesis of vicinal halohydrins

Jinglei Zhang [a], Jie Wang [a], Zhuibai Qiu [a,*], Yang Wang [a,b,*]

[a] Department of Medicinal Chemistry, School of Pharmacy, Fudan University, 826 Zhangheng Road, Shanghai 201203, China
[b] State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, China

ARTICLE INFO

Article history:
Received 18 April 2011
Received in revised form 17 June 2011
Accepted 24 June 2011
Available online 30 June 2011

Keywords:
Chlorohydroxylation
Chlorohydrin
Bromohydroxylation
Bromohydrin
Olefin

ABSTRACT

An efficient method for the synthesis of vicinal chlorohydrin or bromohydrin derivatives has been developed on the basis of direct halohydroxylation of various olefins with electrondonating or withdrawing substituent. The reactions were carried out under mild conditions in the presence of *N*-tosyl-L-threonine (NTsLT) as an acidic additive using chloramine T trihydrate, 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) or *N*-bromoacetamide (AcNHBr) as the halogen source, respectively, affording the corresponding vicinal halohydrins in good to high yields with excellent regio- and stereoselectivities.

1. Introduction

Vicinal halohydrins are extremely versatile building blocks in organic, medicinal, and industrial chemistry and widely used for transformation into epoxides,[1] ketones,[2] halogenated marine natural products,[3] unnatural aminoacids or various chiral auxiliaries.[4] They have been also utilized as the key intermediates for the preparation of homochiral β-adrenergic blockers.[5] The most common method for the preparation of halohydrins involves ring opening of epoxides by hydrogen halides or metal halides.[6] These procedures are generally associated with the formation of byproducts, such as vicinal dihalides and diols[6c,d] and required prior synthesis of epoxides from olefins. Halohydrins can also be directly synthesized by functionalization of alkenes to *vic*-halohydrins with a variety of reagents, such as molecular halogen in combination with water,[7] hypoiodous acid generated in situ from H_5IO_6 in the presence of $NaHSO_3$,[8] *N*-halosuccinimide with water in the presence of β-cyclodextrin, ionic liquid, NH_4OAc or thiourea,[9] metal halide along with an oxidizing agent[10] or *N*,*N*-dibromo-*p*-toluenesulfonamide.[11] However, the existing methodologies usually have the disadvantages of danger of manipulation and toxicity, limited applicability to olefinic substrates, longer reaction time, using expensive reagents including β-cyclodextrin or ionic liquid, and low yields caused by formation of regio-isomers or byproducts. In view of high importance of *vic*-halohydrins and shortcomings of the methodologies mentioned above, the development of new protocol for the practical synthesis of *vic*-halohydrins is highly desirable.

In the course of our recent study on the synthesis of novel coumarin derivatives with anti-HIV activities,[12] we disclosed an efficient method for halohydroxylation of olefin derivatives using chloramine T trihydrate, 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) or *N*-bromoacetamide (AcNHBr) as the halogen source under mild conditions. The remarkable features of the present protocol include high yields, excellent regio- and stereoselectivities, as well as high adaptability of the reaction substrates including the olefins with electrondonating or electron-withdrawing substituent. In the present paper, we would like to report the discovery of this new reaction system and the results on this synthetically and practically useful transformation.

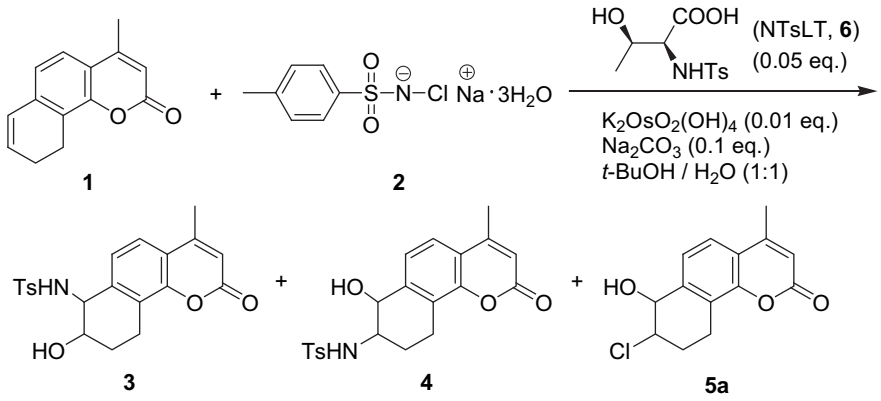
2. Results and discussion

2.1. Chlorohydroxylation of olefins

As part of program aimed toward the development of novel anti-HIV agents, Sharpless aminohydroxylation of 4-methyl-9,10-dihydrobenzo[*h*]coumarin (**1**) was carried out by using chloramine T trihydrate (**2**) as the oxidant (1 equiv) according to the literature procedure (Scheme 1).[13] As expected, the normal

* Corresponding authors. Fax: +86 21 5198 0115; e-mail addresses: zbqiu@shmu.edu.cn, ywang.spfdu@gmail.com, wangyang@shmu.edu.cn.

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.06.077



Scheme 1. The aminohydroxylation of 4-methyl-9,10-dihydrobenzo[*h*]coumarin (**1**).

aminohydroxylation products **3** and **4** were obtained in 55% total yield after stirring for 2 days at room temperature. It is interesting to note that a chlorohydroxylation product 8-chloro-7-hydroxy-4-methyl-7,8,9,10-tetrahydrobenzo[*h*]coumarin (**5a**) was simultaneously isolated in 6% yield, which implied that chloramine T must be involved in the course of reaction as the Cl^+ source. A substantial improvement resulted in selectivity inversion was realized when the reaction was performed by increasing the amount of *N*-tosyl-L-threonine (NTsLT, **6**) employed. It was found that the yield of chlorohydroxylation product (**5a**) was dramatically enhanced to 81% and no products **3**/**4** were isolated when the amount of NTsLT was raised to 2 equiv (Table 1, entry 4). These results clearly demonstrated that NTsLT no longer served as a chiral ligand in the present chlorohydroxylation reaction system and might play the role of an acidic additive. Moreover, when the reaction was carried out in the absence of $K_2OsO_2(OH)_4$ and alkaline Na_2CO_3, chlorohydroxylation product (**5a**) was isolated in 83% yield (entry 5), indicating the dispensability of catalytic amount of $K_2OsO_2(OH)_4$ (0.01 equiv) and alkaline Na_2CO_3 (0.1 equiv) for the efficient chlorohydroxylation.

On the basis of the finding for the chlorohydroxylation of 4-methyl-9,10-dihydrobenzo[*h*]coumarin (**1**) mentioned above, we subsequently take styrene as the standard substrate to investigate the impacts of acidic additive and solvent on the chlorohydroxylation. As shown in Table 2 (entries 1–6), the reaction of styrene occurred to afford 2-chloro-1-phenylethanol (**7**) exclusively in only moderate yields when NTsLT was replaced by other acidic additives. It was found that solvent employed in the process also had significant influence on the yields of chlorohydroxylation products (entries 6–8). The role of the functional groups (−COOH, −OH and −NHTs) of NTsLT were also investigated. If the COOH group of NTsLT was blocked by esterification with CH_3OH, the chlorohydroxylation reaction did not take place at all with this additive (entry 9). If the OH group of NTsLT was esterified with acetyl chloride, the chlorohydroxylated product **7a** was isolated in only 49% yield (entry 10). L-Threonine, which is the NH_2-deprotected NTsLT and mildly alkaline, was also tried as the additive, but no reaction occur at all (entry 11). These results showed that −COOH site of NTsLT and its acidity is crucial to promoting the chlorohydroxylation. The reaction did not occur without any acidic additives, which further confirmed the importance of NTsLT (entry 12). After extensive additive and solvent examination, the reaction carried out in *t*-BuOH/H_2O (v/v 1:1) mixed solvent and in the presence of NTsLT additive turned out to be optimal, affording product **7a** in 92% yield (entry 6).

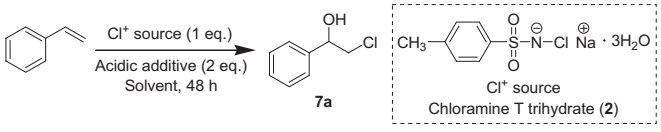
Under the optimized reaction conditions, a panel of olefins was then subjected to chlorohydroxylation. As shown in Table 3, all cyclic olefins examined resulted in the formation of corresponding chlorohydroxylation products in >78% isolated yields with exclusive α-hydroxy-β-chloro regioselectivity. It is worth noting that the

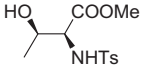
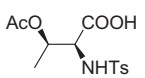
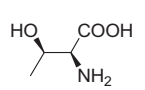
Table 1
Product distribution of **3**/**4** and **5a** in the reaction of **1** with **2** in the presence of different amount of NTsLT (**6**) employed[a]

Entry	Amount of **6** (equiv)	Yield of **5a**[b] (%)	Total yield of **3**+**4**[b] (%)
1	0.05	6	55
2	0.5	60	23
3	1	66	7
4	2	81	—
5[c]	2	83	—

[a] All reactions were carried out under the conditions shown in Scheme 1 with various amount of **6** in 48 h.
[b] Yield of isolated product.
[c] The reaction was carried out in the absence of $K_2OsO_2(OH)_4$ and Na_2CO_3.

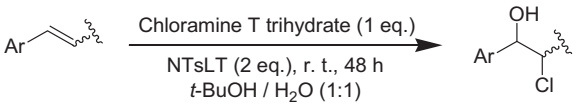
Table 2
Chlorohydroxylation of styrene under various conditions[a]

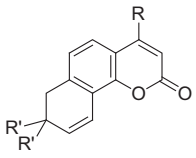
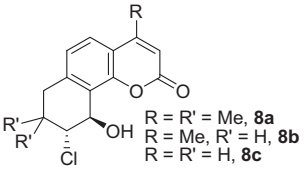
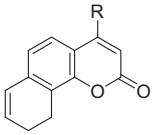
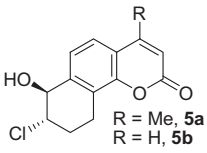
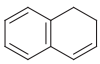
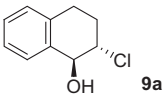
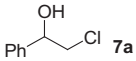
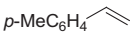
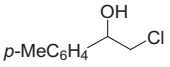
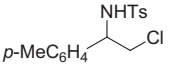
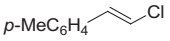
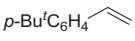
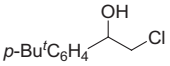
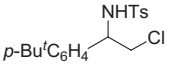
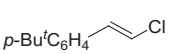
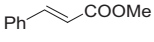
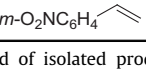


Entry	Acidic additive	Solvent	Yield[b] (%)
1	9% HCl	*t*-BuOH/H_2O (1:1)	55
2	HOAc	*t*-BuOH/H_2O (1:1)	40
3	PTS	*t*-BuOH/H_2O (1:1)	37
4	*dl*-Malic acid	*t*-BuOH/H_2O (1:1)	29
5	H_3PO_4	*t*-BuOH/H_2O (1:1)	35
6	*NTsLT*	*t-BuOH/H2O (1:1)*	*92*
7	NTsLT	CH_3CN/H_2O (1:1)	11
8	NTsLT	*i*-PrOH/H_2O (1:1)	19
9		*t*-BuOH/H_2O (1:1)	—
10		*t*-BuOH/H_2O (1:1)	49[c]
11		*t*-BuOH/H_2O (1:1)	—
12	—	*t*-BuOH/H_2O (1:1)	—

[a] The reaction was carried out under the conditions shown in entry 5 of Table 1 in the presence of various additives and solvents.
[b] The yield determined by HPLC analysis.
[c] The yield of isolated product.

Table 3
Chlorohydroxylation of various olefins with chloramine T trihydrate as the Cl^+ source

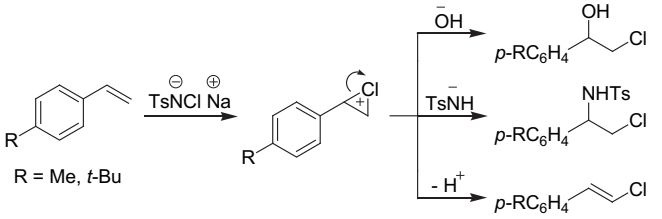


Entry	Substrate	Product	Yield[a]
1		 R = R' = Me, **8a**; R = Me, R' = H, **8b**; R = R' = H, **8c**	80 81 79
2		 R = Me, **5a**; R = H, **5b**	83 84
3		 **9a**	78
4		 **7a**	90
5		 **10a**  **10b**  **10c**	36 20 40
6		 **11a**  **11b**  **11c**	36 (33) 16 (25) 12 (18)
7		—	—
8		—	—

[a] The yield of isolated product after chromatographic purification. The yield shown in parenthesis is obtained by using 2 equiv of chloramine T trihydrate.

reaction of *para*-alkyl substituted styrenes attained α-tosylamino-β-chloro products (**10b**, **11b**) and (2-chlorovinyl)benzene derivatives (**10c**, **11c**) besides the desired chlorohydrins (**10a**, **11a**) in a declined yield of 36% (entries 5 and 6). When chloramine T trihydrate employed was further increased to 2 equiv, the yields of **11b** and **11c** were enhanced to 25% and 18%, respectively, while the yield of chlorohydrins **11a** dropped a little bit (33%). No reaction occurred at all under the same conditions when the substrates have electron-withdrawing group situated at either double-bond or phenyl ring (entries 7 and 8).

A probable mechanistic pathway to explain chemo-, regio-, and stereoselectivity for the reaction of substituted styrenes is depicted in Scheme 2. A three-membered cyclic chloronium ion intermediate is expected to be involved in the reaction on the basis of exclusive trans stereoselectivity in the products of cyclic styrene derivatives (entries 1–3, vide infra Fig. 1). In the case of *para*-alkyl substituted styrene, cyclic chloronium ion intermediate can be formed at the initial stage of the reaction due to electrophilic addition of the Cl^+ ion onto the olefin and will be stabilized by the presence of electrondonating *para*-alkyl substituents. The intermediate undergoes ring opening regioselectively by the nucleophiles, including HO^- or $TsNH^-$, via two competitive S_N2 pathways, affording chlorohydrin and chloroamine, respectively. The chloroamination mechanism proposed here is consistent with that reported by Feng.[14] The formation of (2-chlorovinyl)benzene products were obviously caused by the elimination of H^+ from the chloronium ion intermediate.



Scheme 2. Probable mechanism of the reaction of *para*-alkyl substituted styrenes with chloramine T trihydrate.

In order to elucidate the stereochemistry of two newly-formed chiral centers in the product, the chlorohydrin **5a** was selected to grow a single crystal and its structure was determined by X-ray single crystal analysis. As shown in Fig. 1, OH and Cl obviously take an *anti*-configuration. We deduce that *anti*-addition has occurred in all the rest of the internal olefinic substrates because the reactions proceed via the same mechanistic pathway. Chiral HPLC and $[\alpha]_D$ measurement of product **5a** disclosed that no asymmetric induction was attained in reaction.

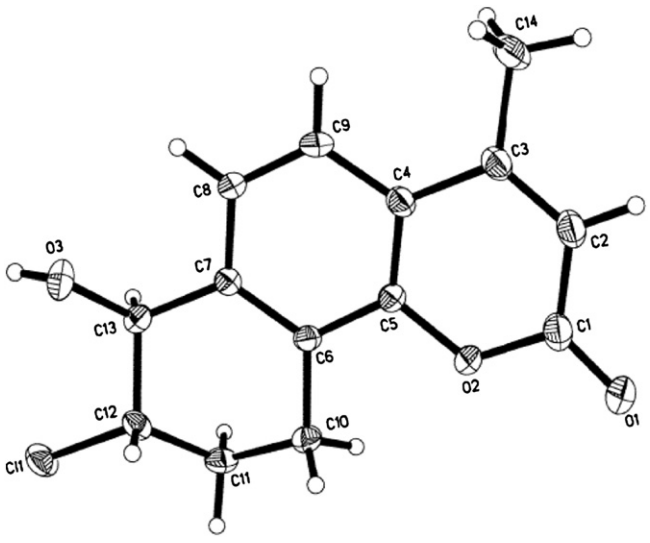
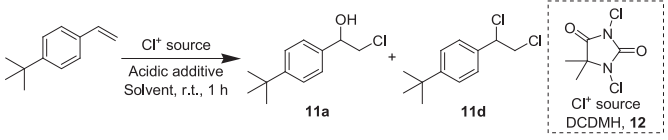


Fig. 1. The X-ray single crystal analysis of 8-chloro-7-hydroxy-4-methyl-7,8,9,10-tetrahydrobenzo[*h*]coumarin (**5a**).

A continuous endeavor was made to overcome the shortcomings of long reaction time and relatively low yields in some cases as shown in Table 3. A more reactive Cl^+ source 1,3-dichloro-5,5-dimethylhydantoin (**12**, DCDMH), which has been used for chlorolactonization reaction,[15] was employed and afforded a faster reaction of about 1 h (Table 4). The chlorohydroxylation of challenging substrate *p*-*tert*-butylstyrene revealed that both the acidic additive and solvent again affected the yields and distributions of products greatly. Employing 1 equiv of benzoic acid as the additive and *t*-BuOH/H_2O (1:1) as the solvent, 1,2-dichloro product (**11d**) was afforded in 51% yield as the major and the chlorohydrin (**11a**) in 18% yield as the minor (Table 4, entries 2). When NTsLT additive was used, α-hydroxy-β-chloro product (**11a**) was attained as the main product. After an exhaustive screening of the amount of acidic additive, mixed solvent and its volume ratio, the best result was obtained in acetone/H_2O (1:2) by employing 1 equiv of DCDMH in the presence of 0.5 equiv of NTsLT additive (Table 4, entry 10), affording chlorohydrin (**11a**) in 65% yield and dichlorinated byproduct (**11d**) in 13% yield. When the volume ratio of acetone/H_2O was changed to 2:1, the yield of chlorohydrin (**11a**) was decreased to 54% yield (entry 11). The reaction did not occur at all in the absence of NTsLT (entry 12), which implies that acidic additive is critically important for the generation of Cl^+ species.

With this new and more efficient chlorohydroxylation system in hand, the scope of the olefin substrates was then examined under the optimized reaction conditions. As shown in Table 5, excellent α-hydroxy-β-chloro regioselectivity and exclusive *anti*-stereoselectivity were observed regardless of cyclic/acyclic olefins and the nature of substituents at the phenyl ring. For the reaction of styrene derivative having electrondonating substituent at phenyl ring, the chloroamination product (**14b**) was also attained besides the normal chlorohydroxylation product (**14a**) (entry 4), probably due to the stabilization of the chloronium ion intermediate by electrondonating MeO group. Compared with chloramine T trihydrate as the Cl^+ source, the more reactive 1,3-dichloro-5,5-dimethylhydantoin (DCDMH, **12**) afforded a faster and more efficient chlorohydroxylation reaction. In particular, the yields and selectivity in the chlorohydroxylation of styrene derivatives were enhanced to a significant extent and less byproduct was detected (Table 5, entries 1–4). The substrates having electron-withdrawing group situated at either double-bond or phenyl ring could also be converted to the corresponding chlorohydrin product in good yields (entries 5 and 7 in Table 5), indicating the superior performance of DCDMH (**12**) as the Cl^+ source to chloramine T (entries 7 and 8 in Table 3). In the reaction of benzo[*h*]chromen-2-one derivative, up to 99% yield of chlorohydroxylation **8b** was obtained in a shorter reaction time

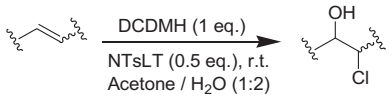
Table 4
Chlorohydroxylation of *p*-*tert*-butylstyrene using DCDMH (**12**) as the Cl^+ source



Entry	Additive (equiv)	DCDMH (equiv)	Solvent	Yield[a] (%)	
				11a	**11d**
1	BA (1)[b]	0.8	*t*-BuOH/H_2O (1:1)	36	21
2	BA (1)[b]	1	*t*-BuOH/H_2O (1:1)	18	51
3	BA (1)[b]	1	*t*-BuOH/H_2O (5:1)	18	48
4	NTsLT (2)	1.1	*t*-BuOH/H_2O (1:1)	50	23
5	NTsLT (2)	1	*t*-BuOH/H_2O (1:5)	—	—
6	NTsLT (1)	1	*t*-BuOH/H_2O (1:1)	51	24
7	NTsLT (1)	1	*t*-BuOH/H_2O (1:2)	55	21
8	NTsLT (0.5)	1	*t*-BuOH/H_2O (1:2)	50	14
9	NTsLT (1)	1	Acetone/H_2O (1:2)	56	12
10	*NTsLT* (0.5)	1	*Acetone/H_2O (1:2)*	*65*	*13*
11	NTsLT (0.5)	1	Acetone/H_2O (2:1)	54	15
12	—	1	Acetone/H_2O (1:2)	—	—

[a] The yield of isolated product.
[b] BA: benzoic acid.

Table 5
Chlorohydroxylation of various olefins using DCDMH (**12**) as the Cl^+ source



Entry	Substrate	Time (h)	Product	Yield[a] (%)
1	Ph	1	OH, Cl, Ph **7a**	93
2	*p*-MeC_6H_4	1	OH, Cl, *p*-MeC_6H_4 **10a**	85
3	*p*-ClC_6H_4	1	OH, Cl, *p*-ClC_6H_4 **13a**	79
4	*p*-$MeOC_6H_4$	1	OH, Cl, *p*-$MeOC_6H_4$ **14a**	62
			Cl, N, O, N, O, Cl, *p*-$MeOC_6H_4$ **14b**	23
5	*m*-$O_2NC_6H_4$	1	OH, Cl, *m*-$O_2NC_6H_4$ **15a**	84
6	Ph, Ph	2	OH, Ph, Ph, Cl **16a**	80
7	Ph, COOMe	36	OH, Ph, COOMe, Cl **17a**	96
8		1	Cl, OH **9a**	79
9[b]	O, O	3	O, O, OH, Cl **8b**	99
10		0.5	OH, Cl **18a**	68

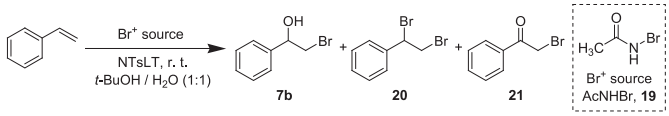
[a] The yield of isolated product after chromatographic purification.
[b] Acetone/H_2O (2:1) mixed solvent was employed for the reaction due to the poor solubility of the substrate.

(Table 5, entry 9). Therefore, DCDMH is obviously a more efficient chlorohydroxylating reagent than chloramine T trihydrate. The olefins with two aromatic or saturated substituents, such as 1,2-diphenylethene and cyclohexene, could also be converted to the corresponding chlorohydrins in 80% and 68%, respectively (entries 6 and 10).

2.2. Bromohydroxylation of olefins

Encouraged by the discovery that this new protocol of chlorohydroxylation using DCDMH as Cl^+ source provided high efficacy for a wide range of olefin substrates with excellent α-hydroxy-β-chloro regioselectivity and exclusive *anti*-stereoselectivity, we subsequently study bromohydroxylation reactions of olefins, an analogous transformation to the chlorohydroxylation. As shown in Table 6, the model bromohydroxylation of styrene proceeded smoothly by using readily available *N*-bromoacetamide (AcNHBr, **19**) as the Br^+ source under various conditions, affording 2-bromo-1-phenylethanol (**7b**) in good to high yields. The bromohydroxylation of styrene using 1.2 equiv of AcNHBr in the presence of 1 equiv of NTsLT as additive turned out to optimal, accomplishing the conversion of substrate in 10 min and affording **7b** in 87% isolated yield (entry 4), which is somewhat superior to that of reaction performed by using NBS as the Br^+ source in 30 min (81%, entry 5). It is obvious that the use of excessive amount of AcNHBr (such as 1.5 or 2 equiv) could result in the formation of byproducts including (1,2-dibromoethyl)benzene (**20**), 2-bromo-1-phenylethanone (**21**) or both, and the formation of bromohydrin (**7b**) was generally quelled (entries 1–3).

Table 6
Bromohydroxylation of styrene with *N*-bromoacetamide (AcNHBr, **19**) as the Br^+ source

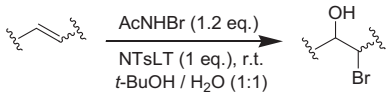


Entry	NTsLT (equiv)	Br^+ source (equiv)	Time (h)	Yield[a] (%)		
				7b	**20**	**21**
1	2	AcNHBr (2)	42	64	9	24
2	2	AcNHBr (2)	1	73	8	—
3	2	AcNHBr (1.5)	0.5	80	4	—
4	*1*	*AcNHBr* (1.2)	*0.2*	*87*	—	—
5	1	NBS (1.2)	0.5	81	—	—

[a] The yield of isolated product after chromatographic purification.

Under the optimized conditions mentioned above, the bromohydroxylation of a variety of substrates were then examined. As shown in Table 7, the reaction of all substrates afforded bromohydroxylation products in good yields with excellent α-hydroxy-β-bromo regioselectivity and exclusive *anti*-selectivity (Table 7). Most of the substituted styrene showed high reactivity to afford bromohydrins with good to excellent yields within 0.5–1 h (entries 1–7). In particular, the reaction of olefins having electron-withdrawing substituents provided the corresponding bromohydrins in good yields (entries 8 and 9) simply by prolonging the reaction time. The cyclic olefins could also be converted to the corresponding bromohydrins in good yields within 30 min (entries 10–12). The *anti*-configuration was determined by analysis of the coupling constant data of protons attached to the carbons bearing –OH and –Br groups of the bromohydrins[11] and further confirmed by structural analysis of X-ray crystallography data of compound **24**, which was esterified from bromohydrin **8d** (Fig. 2).

Table 7
Synthesis of bromohydrins from various olefins



Entry	Substrate	Time (h)	Product	Yield[a] (%)
1	*p*-MeC_6H_4	0.5	*p*-MeC_6H_4 **10d**	77
2	*p*-ClC_6H_4	0.5	*p*-ClC_6H_4 **13b**	84
3	*p*-$MeOC_6H_4$	0.3	*p*-$MeOC_6H_4$ **14c**	77
4	*p*-$Bu^tC_6H_4$	0.3	*p*-$Bu^tC_6H_4$ **11e**	87
5	*m*-$O_2NC_6H_4$	1	*m*-$O_2NC_6H_4$ **15b**	75
6	Ph	1	Ph **22**	88
7	Ph, Ph	1	Ph, Ph **16b**	70
8	Ph, COOMe	6	Ph, COOMe **17b**	86
9	Ph, $COOCH_2Ph$	48	Ph, $COOCH_2Ph$ **23**	81
10		0.4	**9b**	78
11[b]		0.5	**8d**	94
12		0.2	**18b**	62

[a] The yield of isolated product after chromatographic purification.
[b] Acetone/H_2O (2:1) mixed solvent was employed for the reaction due to the poor solubility of the substrate.

3. Conclusion

In summary, an efficient method for chlorohydroxylation and bromohydroxylation of olefins has been established by using chloramine T trihydrate, DCDMH, or AcNHBr as the halogen source in combination with NTsLT as the acidic additive. The significant advantages offered by this method include simple manipulation, fast reaction, and mild conditions, as well as wide adaptability of substrates with high yield and excellent regio- and stereoselectivity (*anti*) of product, and thus providing a better and practical

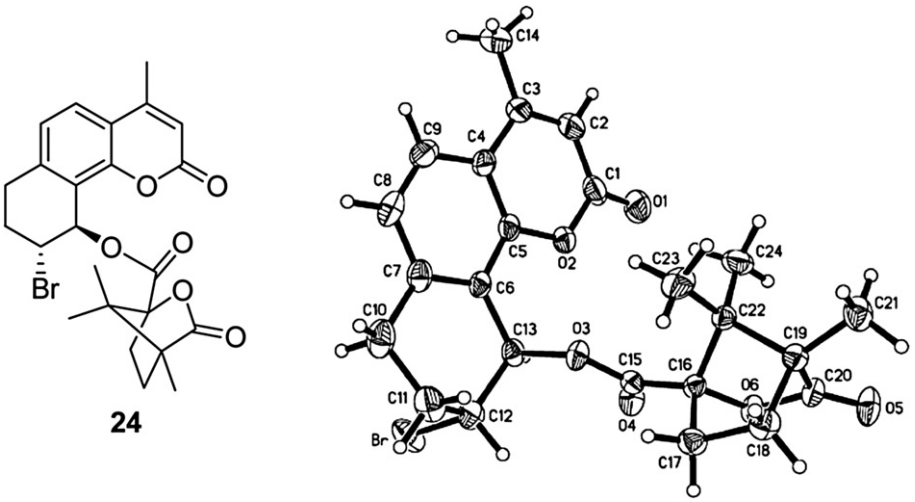


Fig. 2. The structure and X-ray single crystal analysis of (9*R*,10*R*)-9-bromo-10-hydroxy-10-*O*-(−)-camphanoyl-4-methyl-7,8,9,10-tetrahydrobenzo[*h*]chromen-2-one (**24**).

alternative to the existing procedures for the synthesis of vicinal halohydrins.

4. Experimental section

4.1. General procedure for the synthesis of chlorohydrins with chloramine T trihydrate

N-Tosyl-L-threonine (NTsLT, **6**) (546 mg, 2 mmol), which was prepared from L-threonine by following literature procedure,[16] was dissolved in *t*-BuOH/H_2O (1:1 volume ratio, 4 mL), then chloramine T trihydrate (**2**) (282 mg, 1 mmol) and olefin (1 mmol) were added to the solution. The mixture was stirred at room temperature until the reaction was complete (as monitored by TLC). The mixture was extracted with ethyl acetate (3×10 mL) and the combined organic phases were washed with brine (10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude residue was further purified by column chromatography to obtain the corresponding chlorohydrin products.

4.2. General procedure for the synthesis of chlorohydrins with DCDMH

NTsLT (**6**) (137 mg, 0.5 mmol) was dissolved in acetone/H_2O (1:2 volume ratio, 4 mL), then DCDMH (**12**) (197 mg, 1 mmol) and olefin (1 mmol) were added to the solution. The mixture was stirred at room temperature until the reaction was complete (as monitored by TLC). The mixture was extracted with ethyl acetate (3×10 mL) and the combined organic phases were washed with brine (10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude residue was further purified by column chromatography to obtain the corresponding chlorohydrin products.

*4.2.1. 8-Chloro-7-hydroxy-4-methyl-7,8,9,10-tetrahydrobenzo[h] chromen-2-one (**5a**).* Colorless needle crystal, mp 160–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16–2.25 (m, 1H, 9-H), 2.42 (s, 3H, 4-CH_3), 2.49–2.56 (m, 1H, 9-H), 2.88 (s, 1H, −OH), 2.96–3.04 (m, 1H, 10-H), 3.16–3.24 (m, 1H, 10-H), 4.21–4.26 (m, 1H, 8-H), 4.82–4.85 (m, 1H, 7-H), 6.27 (s, 1H, 3-H), 7.49–7.53 (m, 2H, 5-H, 6-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.98, 152.80, 150.87, 139.86, 124.12, 123.88, 122.68, 119.01, 114.99, 73.66, 62.11, 28.25, 21.57, 18.99.

*4.2.2. X-ray single crystal data of 8-chloro-7-hydroxy-4-methyl-7,8,9,10-tetrahydrobenzo[h]chromen-2-one (**5a**).* Crystal with dimensions of 0.496×0.411×0.403 mm for compound **5a** was selected and mounted on a Bruker Smart CCD diffractometer with graphite monochromatized Mo Kα radiation (λ=0.071073 nm). Diffraction data were collected using ω–2θ scans at room temperature (293 K). A perspective view of the structure is depicted in Fig. 1. Empirical formula: $C_{14}H_{13}ClO_3$. Formula weight: 264.69. Crystal system: orthorhombic. Space group: $P2_12_12_1$. Unit cell dimensions: a=5.1157 (10) Å, b=8.0771 (15) Å, c=29.431 (6) Å. V=1216.1 (4) Å^3. Theta range for data collection is from 1.38 to 26.49°. Z=4. D_c=1.446 g/cm^3. F (000)=552. Refinement method: full-matrix least-squares on F^2. Goodness-of-fit on F^2: 1.040. Final R indices [$I>2\sigma(I)$]: 0.0626, 0.1493. R indices (all data): 0.0662, 0.1523. Largest diff. peak and hole: 0.562 and −0.316 e/Å^3.

*4.2.3. 2-Chloro-1-phenylethanol (**7a**).* Colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.04 (br, 1H, −OH), 3.54–3.68 (m, 2H, 2-H), 4.78–4.82 (m, 1H, 1-H), 7.28–7.33 (m, 5H, Ph–H).

*4.2.4. 9-Chloro-10-hydroxy-4,8,8-trimethyl-7,8,9,10-tetrahydrobenzo [h]chromen-2-one (**8a**).* White solid, mp 178–181 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (s, 3H, 8-CH_3), 1.22 (s, 3H, 8-CH_3), 2.41 (s, 3H, 4-CH_3), 2.82 (s, 2H, 7-H), 4.07–4.12 (m, 2H, 9-H, −OH), 5.25–5.27 (m, 1H, 10-H), 6.24 (s, 1H, 3-H), 7.03 (d, J=8.4 Hz, 1H, 6-H), 7.48 (d, J=7.8 Hz, 1H, 5-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.38, 153.23, 152.44, 140.25, 124.86, 124.50, 124.29, 118.46, 114.04, 72.45, 70.83, 42.96, 36.31, 21.67, 19.09. MS (EI) m/z (%): 292 (M^+, 35.03), 239 (26.27), 202 (91.26), 174 (75.76), 171 (59.21), 155 (48.73), 146 (53.46), 91 (100.00). HRMS: calcd mass for $C_{16}H_{17}O_3Cl$ 292.0866, found 292.0864.

*4.2.5. 9-Chloro-10-hydroxy-4-methyl-7,8,9,10-tetrahydrobenzo[h] chromen-2-one (**8b**).* White solid, mp 187 °C (decomposed). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12–2.17 (m, 1H, 8-H), 2.43 (s, 3H, 4-CH_3), 2.45–2.52 (m, 1H, 8-H), 2.81–2.91 (m, 1H, 7-H), 3.14–3.19 (m, 1H, 7-H), 3.71 (br, 1H, −OH), 4.51–4.53 (m, 1H, 9-H), 5.35 (d, J=2.4 Hz, 1H, 10-H), 6.26 (s, 1H, 3-H), 7.12 (d, J=8.0 Hz, 1H, 6-H), 7.50 (d, J=8.4 Hz, 1H, 5-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.97, 153.37, 152.89, 141.01, 125.06, 123.99, 123.49, 118.18, 114.01, 65.90, 58.57, 29.88, 24.75, 19.01. MS (EI) m/z (%): 264 (M^+, 5.59), 171 (37.04), 155 (33.81), 108 (13.64), 107 (22.22), 91 (100.00), 89 (10.23), 65 (28.44), 63 (11.98). HRMS: calcd mass for $C_{14}H_{13}O_3Cl$ 264.0553, found 264.0559.

*4.2.6. 9-Chloro-10-hydroxy-7,8,9,10-tetrahydrobenzo[h]chromen-2-one (**8c**).* White solid, mp 191–194 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.16–2.18 (m, 1H, 8-H), 2.45–2.50 (m, 1H, 8-H), 2.86–2.92 (m, 1H, 7-H), 3.14–3.19 (m, 1H, 7-H), 3.38 (br, 1H, −OH), 4.51–4.54 (m,

1H, 9-H), 5.37 (d, *J*=1.5 Hz, 1H, 10-H), 6.39 (d, *J*=6.9 Hz, 1H, 3-H), 7.10 (d, *J*=6.0 Hz, 1H, 6-H), 7.37 (d, *J*=6.0 Hz, 1H, 5-H), 7.70 (d, *J*=7.2 Hz, 1H, 4-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.74, 151.29, 143.50, 139.75, 125.87, 123.82, 123.79, 117.73, 116.51, 73.67, 62.12, 28.27, 21.38. MS (EI) *m*/*z* (%): 252 (17.18), 250 (M^+, 50.50), 197 (82.44), 188 (78.24), 160 (100.00), 132 (49.02), 131 (28.89), 115 (15.07), 91 (26.32). HRMS calcd mass for $C_{13}H_{11}ClO_3$ 250.0397, found 250.0395.

*4.2.7. 8-Chloro-7-hydroxy-7,8,9,10-tetrahydrobenzo[h]chromen-2-one (**5b**).* White solid, mp 169–171 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16–2.26 (m, 1H, 9-H), 2.49–2.56 (m, 1H, 9-H), 2.96–3.04 (m, 1H, 10-H), 3.18–3.25 (m, 1H, 10-H), 4.20–4.26 (m, 1H, 8-H), 4.84 (t, *J*=7.7 Hz, 1H, 7-H), 6.42 (d, *J*=9.4 Hz, 1H, 3-H), 7.40 (d, *J*=8.2 Hz, 1H, 6-H), 7.51 (d, *J*=7.8 Hz, 1H, 5-H), 7.70 (d, *J*=9.8 Hz, 1H, 4-H). MS (EI) *m*/*z* (%): 250 (M^+, 34.50), 215 (17.37), 198 (14.15), 197 (42.57), 188 (100.00), 187 (44.58), 159 (25.73), 131 (15.52). Elemental Anal. Calcd for $C_{13}H_{11}O_3Cl$: C, 62.29; H, 4.42; Cl, 14.14. Found: C, 62.29; H, 4.43; Cl, 14.82.

*4.2.8. 2-Chloro-1,2,3,4-tetrahydro-1-naphthol (**9a**).* White solid, mp 92–93 °C (lit.[17] 91 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12–2.22 (m, 1H, 3-H), 2.39–2.46 (m, 1H, 3-H), 2.53 (d, *J*=4.5 Hz, 1H, 2-H), 2.88–3.03 (m, 2H, 4-H), 4.20–4.25 (m, 1H, 1-H), 4.78–4.81 (m, 1H, –OH), 7.10–7.12 (m, 1H, 7-H), 7.21–7.27 (m, 2H, 5-H, 8-H), 7.52–7.55 (m, 1H, 6-H).

*4.2.9. 2-Chloro-1-p-tolylethanol (**10a**).* Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H, $-CH_3$), 2.63 (s, 1H, –OH), 3.62–3.74 (m, 2H, 2-H), 4.86–4.88 (m, 1H, 1-H), 7.19 (d, *J*=7.82 Hz, 2H, Ar–H), 7.28 (d, *J*=8.21 Hz, 2H, Ar–H).

*4.2.10. N-(2-Chloro-1-p-tolylethyl)-4-methylbenzenesulfonamide (**10b**).* White solid, mp 130–131 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H, $-CH_3$), 2.40 (s, 3H, $-CH_3$), 3.67–3.76 (m, 2H, $-CH_2Cl$), 4.49–4.53 (m, 1H, Ar–CH), 5.04 (d, *J*=6.26 Hz, 1H, –NH), 7.00 (d, *J*=8.21 Hz, 2H, Ar–H), 7.06 (d, *J*=7.82 Hz, 2H, Ar–H), 7.21 (d, *J*=8.21 Hz, 2H, Ar–H), 7.63 (d, *J*=8.22 Hz, 2H, Ar–H).

*4.2.11. 1-(2-Chlorovinyl)-4-methylbenzene (**10c**).* Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H, $-CH_3$), 6.21 (d, *J*=8.22 Hz, 0.25H, (*Z*)-2′-H), 6.57–6.61 (m, 1H, 1′-H), 6.80 (d, *J*=13.69 Hz, 0.75H, (*E*)-2′-H), 7.13 (d, *J*=8.22 Hz, 2H, Ar–H), 7.19 (d, *J*=7.83 Hz, 2H, Ar–H).

*4.2.12. 1-(4-tert-Butylphenyl)-2-chloroethanol (**11a**).* Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 9H, $-CH_3$), 2.63 (d, *J*=2.35 Hz, 1H, –OH), 3.64–3.77 (m, 2H, 2-H), 4.89 (d, *J*=9.00 Hz, 1H, 1-H), 7.33 (d, *J*=8.61 Hz, 2H, Ar–H), 7.41 (d, *J*=8.21 Hz, 2H, Ar–H).

*4.2.13. N-(1-(4-tert-Butylphenyl)-2-chloroethyl)-4-methylbenzenesulfonamide (**11b**).* White solid, mp 115–117 C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 9H, $-CH_3$), 2.38 (s, 3H, $-CH_3$), 3.73 (d, *J*=5.87 Hz, 2H, $-CH_2Cl$), 4.55–4.59 (m, 1H, Ar–CH), 5.24 (d, *J*=5.26 Hz, 1H, –NH), 7.02 (d, *J*=8.21 Hz, 2H, Ar–H), 7.16 (d, *J*=7.82 Hz, 2H, Ar–H), 7.20–7.23 (m, 2H, Ar–H), 7.59 (d, *J*=8.61 Hz, 2H, Ar–H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.44, 143.48, 137.18, 134.17, 129.60, 127.40, 126.76, 125.67, 58.38, 48.06, 34.68, 31.44, 21.71. ESI-MS *m*/*z* (%): 383.0 ($M+NH_4^+$, 30). HRMS: calcd mass for $C_{19}H_{24}ClNNaO_2S$ 388.11085, found 388.11238.

*4.2.14. 1-tert-Butyl-4-(2-chlorovinyl)benzene (**11c**).* Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 9H, $-CH_3$), 6.24 (d, *J*=8.22 Hz, 0.25H, (*Z*)-2′-H), 6.60–6.64 (m, 1H, 1′-H), 6.83 (d, *J*=13.70 Hz, 0.75H, (*E*)-2′-H), 7.26 (d, *J*=8.21 Hz, 2H, Ar–H), 7.37 (d, *J*=7.83 Hz, 2H, Ar–H).

*4.2.15. 1-tert-Butyl-4-(1,2-dichloroethyl)benzene (**11d**).* Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 9H, $-CH_3$), 3.91–4.02 (m, 2H, $-CH_2Cl$), 5.00 (t, *J*=7.43, 7.04 Hz, 1H, –CHCl–), 7.34 (d, *J*=8.21 Hz, 2H, Ar–H), 7.42 (d, *J*=8.61 Hz, 2H, Ar–H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.45, 135.18, 127.26, 125.99, 62.05, 48.64, 34.90, 31.47. MS (EI) *m*/*z* (%): 230 (M^+, 15.70), 217 (64.37), 215 (100.00), 181 (25.10), 145 (19.52), 128 (17.81), 151 (13.98), 115 (17.41). HRMS calcd mass for $C_{12}H_{16}Cl_2$ 230.0629, found 230.0625.

*4.2.16. 2-Chloro-1-(4-chlorophenyl)ethanol (**13a**).* Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 (br, 1H, –OH), 3.58–3.73 (m, 2H, 2-H), 4.86–4.89 (m, 1H, 1-H), 7.31–7.36 (m, 4H, Ar–H).

*4.2.17. 2-Chloro-1-(4-methoxyphenyl)ethanol (**14a**).* Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (s, 1H, –OH), 3.61–3.72 (m, 2H, 2-H), 3.81 (s, 3H, $-OCH_3$), 4.85 (d, *J*=8.25 Hz, 1H, 1-H), 6.90 (d, *J*=8.55 Hz, 2H, Ar–H), 7.31 (d, *J*=8.56 Hz, 2H, Ar–H).

*4.2.18. 1-Chloro-3-(2-chloro-1-(4-methoxyphenyl)ethyl)-5,5-dimethylimidazolidine-2,4-dione (**14b**).* White solid, mp 76–77 C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 6H, CH_3), 3.79 (s, 3H, CH_3O), 3.87 (dd, *J*=5.09, 11.74 Hz, 1H, CH_2), 4.71 (t, *J*=11.74 Hz, 1H, CH), 5.32 (dd, *J*=5.09, 11.74 Hz, 1H, CH_2), 6.87 (d, *J*=9.00 Hz, 2H, Ar–H), 7.41 (d, *J*=8.61 Hz, 2H, Ar–H). MS (EI) *m*/*z* (%): 330 (M^+, 6.47), 281 (20.00), 260 (38. 71), 231 (100.00), 175 (28.15), 162 (62.79), 134 (12.93), 91 (11.40).

*4.2.19. 2-Chloro-1-(3-nitrophenyl)ethanol (**15a**).* Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.93 (br, 1H, –OH), 3.64–3.69 (m, 1H, 2-H), 3.80 (dd, *J*=11.35, 3.52 Hz, 1H, 2-H), 5.04 (dd, *J*=8.22, 3.52 Hz, 1H, 1-H), 7.57 (t, *J*=7.83 Hz, 1H, 5′-H), 7.75 (d, *J*=7.43 Hz, 1H, 6′-H), 8.18–8.21 (m, 1H, 4′-H), 8.29 (s, 1H, 2′-H).

*4.2.20. 2-Chloro-1,2-diphenylethanol (**16a**)*[9d]. *syn*: Colorless oil, yield 33%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.05 (d, *J*=2.74 Hz, 1H, –OH), 4.95 (dd, *J*=2.35, 8.61 Hz, 1H, 1-H), 5.01 (d, *J*=8.61 Hz, 1H, 2-H), 7.09–7.12 (m, 2H, Ar–H), 7.16–7.24 (m, 8H, Ar–H). *anti*: Colorless oil, yield 47%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (br, 1H, –OH), 5.01 (d, *J*=6.65 Hz, 1H, 1-H), 5.09 (d, *J*=6.26 Hz, 1H, 2-H), 7.27–7.35 (m, 10H, Ar–H).

*4.2.21. Methyl 2-chloro-3-hydroxy-3-phenylpropanoate (**17a**).* Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.04 (d, *J*=4.30 Hz, 1H, –OH), 3.80 (s, 3H, $-OCH_3$), 4.39 (d, *J*=7.82 Hz, 1H, 2-H), 5.03–5.06 (m, 1H, 3-H), 7.35–7.40 (m, 5H, Ar–H).

*4.2.22. 2-Chlorocyclohexanol (**18a**).* Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25–1.32 (m, 4H, $-CH_2-$), 1.63–1.75 (m, 2H, $-CH_2-$), 2.09–2.12 (m, 1H, $-CH_2-$), 2.20–2.24 (m, 1H, $-CH_2-$), 2.44 (br, 1H, –OH), 3.41–3.54 (m, 1H, –CH–), 3.69–3.75 (m, 1H, –CH–).

4.3. General procedure for the synthesis of bromohydrins with AcNHBr

NTsLT (**6**) (273 mg, 1 mmol) was dissolved in *t*-BuOH/H_2O (1:1, 4 mL), then AcNHBr (**19**) (165 mg, 1.2 mmol) and olefin (1 mmol) were added to the solution. The mixture was stirred at room temperature. When the yellow color of the mixture faded, the reaction was complete (also monitored by TLC). Na_2SO_3 (50 mg) was added to the mixture, then extracted with ethyl acetate (3×10 mL) and the organic phases were washed with brine (10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude residue was further purified by column chromatography to obtain the corresponding bromohydrin products.

*4.3.1. 2-Bromo-1-phenylethanol (**7b**).* Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.72 (d, J=2.44, 1H, −OH), 3.58–3.72 (m, 2H, 2-H), 4.97–5.00 (m, 1H, 1-H), 7.38–7.45 (m, 5H, Ar–H).

*4.3.2. (1,2-Dibromoethyl)benzene (**20**).* White solid, mp 74–75 °C (lit.[18] 72 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (s, 2H, $-CH_2Br$), 5.13–5.17 (m, 1H, −CHBr−), 7.35–7.42 (m, 5H, Ar–H).

*4.3.3. 2-Bromo-1-phenylethanone (**21**).* White solid, mp 49–50 °C (lit.[18] 48 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00–4.10 (m, 2H, $-CH_2Br$), 7.50 (t, J=7.31, 8.29 Hz, 2H, 3′-H, 5′-H), 7.60–7.64 (m, 1H, 4′-H), 7.99 (d, J=8.29 Hz, 2H, 2′-H, 6′-H).

*4.3.4. 2-Bromo-1-p-tolylethanol (**10d**).* Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H, $-CH_3$), 2.61 (d, J=2.35 Hz, 1H, −OH), 3.51–3.64 (m, 2H, 2-H), 4.90 (d, J=9.00 Hz, 1H, 1-H), 7.19 (d, J=7.83 Hz, 2H, Ar–H), 7.27 (d, J=8.22 Hz, 2H, Ar–H).

*4.3.5. 2-Bromo-1-(4-chlorophenyl)ethanol (**13b**).* White solid, mp 61–63 °C (lit.[19] 61–62 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.65 (d, J=2.93 Hz, 1H, −OH), 3.49–3.64 (m, 2H, 2-H), 4.91–4.93 (m, 1H, 1-H), 7.32–7.38 (m, 4H, Ar–H).

*4.3.6. 2-Bromo-1-(4-methoxyphenyl)ethanol (**14c**).* Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61 (d, J=2.56 Hz, 1H, −OH), 3.50–3.62 (m, 2H, 2-H), 3.81 (s, 3H, $-OCH_3$), 4.88 (d, J=8.79 Hz, 1H, 1-H), 6.90 (dd, J=6.76, 1.83 Hz, 2H, Ar–H), 7.30 (dd, J=6.78, 1.83 Hz, 2H, Ar–H).

*4.3.7. 2-Bromo-1-(4-tert-butylphenyl)ethanol (**11e**).* Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (s, 9H, $-CH_3$), 2.59 (d, J=2.92 Hz, 1H, −OH), 3.53–3.65 (m, 2H, 2-H), 4.89–4.93 (m, 1H, 1-H), 7.31–7.41 (m, 4H, Ar–H).

*4.3.8. 2-Bromo-1-(3-nitrophenyl)ethanol (**15b**).* Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85 (br, 1H, −OH), 3.53–3.57 (m, 1H, 2-H), 3.69 (dd, J=10.56, 3.52 Hz, 1H, 2-H), 5.05 (dd, J=8.22, 3.52 Hz, 1H, 1-H), 7.57 (t, J=8.21 Hz, 1H, 5′-H), 7.74 (d, J=7.43 Hz, 1H, 6′-H), 8.19–8.21 (m, 1H, 4′-H), 8.29 (s, 1H, 2′-H).

*4.3.9. 1-Bromo-2-phenyl-2-propanol (**22**).* Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68 (s, 3H, $-CH_3$), 2.58 (s, 1H, −OH), 3.69–3.78 (m, 2H, 1-H), 7.28–7.48 (m, 5H, Ar–H).

*4.3.10. 2-Bromo-1,2-diphenylethanol (**16b**).* White solid, mp 85–86 °C (lit.[20] 83–86 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (d, J=3.13 Hz, 1H, −OH), 5.10 (d, J=6.65 Hz, 1H, 2-H), 5.20–5.21 (m, 1H, 1-H), 7.30–7.40 (m, 10H, Ar–H).

*4.3.11. Methyl 2-bromo-3-hydroxy-3-phenylpropanoate (**17b**).* Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.22 (br, 1H, −OH), 3.80 (s, 3H, $-OCH_3$), 4.38 (d, J=8.22 Hz, 1H, 2-H), 5.08 (d, J=8.22 Hz, 1H, 3-H), 7.34–7.41 (m, 5H, Ar–H).

*4.3.12. Benzyl 2-bromo-3-hydroxy-3-phenylpropanoate (**23**).* Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.16 (d, J=5.48 Hz, 1H, −OH), 4.43 (d, J=8.21 Hz, 1H, 2-H), 5.08–5.12 (m, 1H, 3-H), 5.19–5.26 (m, 2H, $-CH_2Ar$), 7.31–7.38 (m, 10H, Ar–H).

*4.3.13. 2-Bromo-1,2,3,4-tetrahydro-1-naphthol (**9b**).* Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25–2.33 (m, 1H, 3-H), 2.49–2.55 (m, 2H, 3-H, −OH), 2.93–2.98 (m, 2H, 4-H), 4.34–4.39 (m, 1H, 2-H), 4.90–4.93 (m, 1H, 1-H), 7.10–7.12 (m, 1H, 7-H), 7.22–7.25 (m, 2H, 5-H, 8-H), 7.51–7.53 (m, 1H, 6-H).

*4.3.14. 9-Bromo-10-hydroxy-4-methyl-7,8,9,10-tetrahydrobenzo[h]chromen-2-one (**8d**).* White solid, mp 194–196 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17–2.20 (m, 1H, 8-H), 2.43 (s, 3H, $-CH_3$), 2.49–2.57 (m, 1H, 8-H), 2.88–2.95 (m, 1H, 7-H), 3.15–3.23 (m, 1H, 7-H), 4.61–4.62 (m, 1H, 9-H), 5.50 (d, J=2.74 Hz, 1H, 10-H), 6.27 (s, 1H, 3-H), 7.13 (d, J=8.22 Hz, 1H, 6-H), 7.50 (d, J=8.22 Hz, 1H, 5-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.83, 153.30, 152.80, 140.84, 125.06, 124.06, 123.44, 118.21, 114.07, 66.27, 51.26, 25.85, 25.25, 19.02. MS (EI) m/z (%): 229 (93.04), 211 (100.00), 212 (79.30), 174 (73.83), 146 (83.17), 128 (37.44), 115 (59.74), 91 (46.17). HRMS: calcd mass for $C_{14}H_{13}O_3Br$ 308.0048, found 308.0045.

*4.3.15. 2-Bromocyclohexanol (**18b**).* Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23–1.37 (m, 4H, $-CH_2-$), 1.76–1.84 (m, 2H, $-CH_2-$), 2.10–2.13 (m, 1H, $-CH_2-$), 2.30–2.35 (m, 1H, $-CH_2-$), 2.66 (br, 1H, −OH), 3.56–3.62 (m, 1H, −CH−), 3.85–3.92 (m, 1H, −CH−).

*4.3.16. X-ray single crystal data of (9R,10R)-9-bromo-10-hydroxy-10-O-(−)-camphanoyl-4-methyl-7,8,9,10-tetrahydrobenzo[h]chromen-2-one (**24**).* Crystal with dimensions of 0.356×0.193 ×0.147 mm for compound **24** was selected and mounted on a Bruker Smart CCD diffractometer with graphite monochromatized Mo Kα radiation (λ=0.071073 nm). Diffraction data were collected using ω–2θ scans at room temperature (293 K). A perspective view of the structure is depicted in Fig. 2. Empirical formula: $C_{24}H_{25}BrO_6$. Formula weight: 489.35. Crystal system: orthorhombic. Space group: $P2_12_12_1$. Unit cell dimensions: a=6.1497 (5) Å, b=11.6780 (10) Å, c=31.186 (3) Å. V=2239.6 (3) Å^3. Theta range for data collection is from 1.31 to 27.50°. Z=4. D_c=1.461 g/cm^3. F (000)=1008. Refinement method: full-matrix least-squares on F^2. Goodness-of-fit on F^2: 0.898. Final R indices [$I>2\sigma(I)$]: 0.0345, 0.0685. R indices (all data): 0.0529, 0.0780. Largest diff. peak and hole: 0.504 and −0.237 e/Å^3.

Acknowledgements

Financial support from the National Natural Science Foundation of China (No. 20972033), National Drug Innovative Program (Grant No. 2009ZX09301-011), and the State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences (SIMM1004KF-08) is gratefully acknowledged.

References and notes

1. Smith, M. B.; March, J. *Advanced Organic Chemistry*, 5th ed.; Wiley-Interscience: New York, NY, 2001; p 478, and references cited therein.
2. Dolence, D.; Harej, M. *J. Org. Chem.* **2002**, *67*, 312.
3. Erikson, R. E. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic: New York, NY, 1986; Vol. V, p 131.
4. (a) Watson, K. G.; Fung, Y. M.; Gredley, M.; Bird, G. J.; Jackson, W. R.; Gountzos, H.; Matthews, B. R. *J. Chem. Soc., Chem. Commun.* **1990**, 1018; (b) Akiyama, Y.; Fukuhara, T.; Hara, S. *Synlett* **2003**, 1530.
5. Berinakalti, H. S.; Banerji, A. A. *J. Org. Chem.* **1992**, *57*, 6003.
6. (a) Smith, J. G.; Fieser, M. *Fieser's Reagent for Organic Synthesis*; John: New York, NY, 1990; Vols. 1–12; (b) Shimizu, M.; Yoshida, A.; Fijisawa, T. *Synlett* **1992**, 204; (c) Bonini, C.; Righi, G. *Synthesis* **1994**, 225; (d) Majetich, G.; Hicks, R.; Reister, S. *J. Org. Chem.* **1997**, *62*, 4321; (e) Ranu, B. C.; Banerjee, S. *J. Org. Chem.* **2005**, *70*, 4517; (f) Das, B.; Krishnaiah, M.; Venkateswarlu, K. *Tetrahedron Lett.* **2006**, *47*, 4457; (g) Surendra, K.; Krishnaveni, N. S.; Kumar, V. P.; Nageswar, Y. V. D.; Rama Rao, K. *Lett. Org. Chem.* **2005**, *2*, 652.
7. Rolston, J. H.; Yates, K. *J. Am. Chem. Soc.* **1969**, *91*, 1469.
8. Masuda, H.; Takase, K.; Nishio, M.; Hasegawa, A.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1994**, *59*, 5550.
9. (a) Narender, M.; Somi Reddy, M.; Nageswar, Y. V. D.; Rama Rao, K. *J. Mol. Catal. A: Chem.* **2006**, *258*, 10; (b) Yadav, J. S.; Reddy, B. V. S.; Baishya, G.; Harshavardhan, S. J.; Janardhana Chary, Ch.; Gupta, M. K. *Tetrahedron Lett.* **2005**, *46*, 3569; (c) Das, B.; Venkateswarlu, K.; Damodar, K.; Suneel, K. *J. Mol. Catal. A: Chem.* **2007**, *269*, 17; (d) Bentley, P. A.; Mei, Y.; Du, J. *Tetrahedron Lett.* **2008**, *49*, 1425.
10. (a) Kabalka, G. W.; Yang, K.; Reddy, N. K.; Narayana, C. *Synth. Commun.* **1998**, *28*, 925; (b) Dewkar, G. K.; Narina, S. V.; Sudalai, A. *Org. Lett.* **2003**, *5*, 4501.
11. Phukan, P.; Chakraborty, P.; Kataki, D. *J. Org. Chem.* **2006**, *71*, 7533.
12. Wang, Y.; Huang, S. X.; Xia, P.; Xia, Y.; Yang, Z. Y.; Kilgore, N.; Morris-Natschke, S. L.; Lee, K. H. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4316.

13. Andersson, M. A.; Epple, R.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 472.
14. (a) Cai, Y.; Liu, X.; Hui, Y.; Jiang, J.; Wang, W.; Chen, W.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 6160; (b) Cai, Y.; Liu, X.; Jiang, J.; Chen, W.; Lin, L.; Feng, X. *J. Am. Chem. Soc.* **2011**, *133*, 5636.
15. Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *J. Am. Chem. Soc.* **2010**, *132*, 3298.
16. Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1988**, *53*, 2367.
17. Ros, A.; Magriz, A.; Dirtrich, H.; Fernandez, R.; Alvarez, E.; Lassaletta, J. M. *Org. Lett.* **2006**, *8*, 127.
18. Manickam, M. C. D.; Annalakshmi, S.; Pitchumani, K.; Srinivasan, C. *Org. Biomol. Chem.* **2005**, *3*, 1008.
19. Lutz, R. E.; Allison, R. K.; Ashburn, G.; Bailey, P. S.; Clark, M. T.; Codington, J. F.; Deinet, A. J.; Freek, J. A.; Jordan, R. H.; Leake, N. H.; Martin, T. A.; Nicodemus, K. C.; Rowlett, R. J., Jr.; Shearer, N. H., Jr.; Smith, J. D.; Wilson, J. W. *J. Org. Chem.* **1947**, *12*, 617.
20. Bar, S. *Can. J. Chem.* **2010**, *88*, 605.