Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 3073–3077

Lewis acid catalyzed asymmetric halohydrin reactions of chiral α,β-unsaturated carboxylic acid derivatives with *N*-halosuccinimide (NXS) as the halogen source

Saumen Hajra,* Manishabrata Bhowmick and Ananta Karmakar

Department of Chemistry, Indian Institute of Technology, Kharagpur 721302, India

Received 20 January 2005; revised 21 February 2005; accepted 1 March 2005
Available online 18 March 2005

Abstract—Lewis acid catalyzed asymmetric halohydrin reactions—(halohydroxylation as well as halomethoxylation) of chiral α,β-unsaturated carboxylic acid derivatives were performed using *N*-halosuccinimide (NXS; X = Br, I) as the halogen source. Regio- and *anti*-selectivity of 100% and moderate to good diastereoselectivity with good yields were observed when Oppolzer's sultam was used as the chiral auxiliary. Among the Lewis acids, $Yb(OTf)_3$ was found to be the best catalyst. Alkenoyl and cinnamoyl substrates smoothly underwent bromohydrin reactions and the more electron-rich cinnamoyl substrates preferred to undergo iodohydrin reactions. However, electron-deficient cinnamoyl substrates did not respond to this Lewis acid catalyzed halohydrin reaction with NXS (X = Cl, Br, I).

The 1,2-halo functionalization of olefins, for example, halohydrination, (halohydroxylation and haloalkoxylation) is an important transformation in organic chemistry.[1] The product halogen-containing compounds are versatile for the synthesis of pharmaceuticals, dyes, flame retardants, agrochemicals and speciality chemicals.[2] The study of catalytic, highly regioselective and asymmetric halohydrin forming reactions of olefins, especially of electron-deficient olefins, still remains an important challenge to organic chemists.[3]

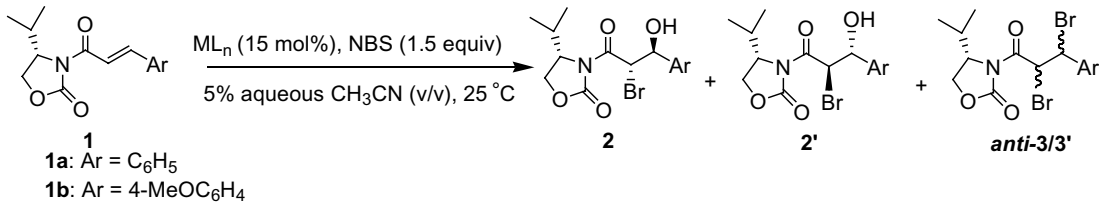
Regioselective and asymmetric halohydrin formation of α,β-unsaturated carboxylic acid derivatives can provide chiral carboxyhalohydrins and α-halo-β-hydroxy/alkoxy carboxylic acid derivatives. These are versatile and useful synthetic intermediates because of their transformations to a variety of important compounds. These moieties are also either present in or are precursors to biologically active compounds.[4,5] In our efforts to provide new asymmetric methods for the halohydrin forming reactions of α,β-unsaturated carboxylic acid derivatives,[6] we describe in this Letter, a Lewis acid catalyzed asymmetric halohydrin reaction, a halohydroxylation as well as halomethoxylation, of chiral α,β-unsaturated carboxylic acid derivatives using *N*-halosuccinimide (NXS; X = Br, I) as the halogen source, in which 100% regioselectivity and with diastereoselectivities of up to 82:18 of the *anti*-α-halo-β-hydroxy/methoxy carbonyl compounds are demonstrated with good yields.

It is known in the literature that α,β-unsaturated carbonyl compounds undergo halohydrin forming reactions with NBS/NIS in the presence of H_2SO_4.[5b,d,7] Initial studies of halohydroxylation of *N*-cinnamoyl-2-oxazolidinone **1a**[8] with NBS/NIS in different aqueous organic solvents such as CH_3COCH_3, CH_3CN, THF, 1,4-dioxane, DME, DMF and DMSO at 25 °C (rt) showed that in aqueous CH_3CN only, **1a** underwent bromohydroxylation. It gave a mixture of the carboxybromohydrins **2a** and **2a′** and the dibromocarbonyl compounds **3a**/**3a′** after 26 h when an excess of NBS (2.5 equiv) was used and the same reaction in the presence of H_2SO_4 gave a mixture of products within 6 h. These observations prompted us to search for an effective catalyst for the asymmetric halohydrin forming reactions of chiral α,β-unsaturated carbonyl compounds with NBS. We screened different Lewis acids as catalysts for this halohydrin forming reaction (Table 1). The

Keywords: Lewis acid; Catalyst; Asymmetric; Halohydrin; Halohydroxylation; Halomethoxylation; *N*-Halosuccinimide (NXS); (2*R*)-*N*-Enoylbornanesultam; α-Halo-β-hydroxy/methoxycarboxylic acid derivatives.
* Corresponding author. Tel.: +91 3222 283340; fax: +91 3222 255303; e-mail: shajra@chem.iitkgp.ernet.in

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.03.014

Table 1. Lewis acid catalysts for the halohydroxylation of **1** with NBS[a]



1
1a: Ar = C_6H_5
1b: Ar = 4-$MeOC_6H_4$

2 **2'** ***anti*-3/3'**

Entry	Substrate	ML_n	*t* (h)	Ratio[b] (**2**+**2′**:**3**/**3′**)	dr[b] (**2**:**2′**)	Yield[c] (%)
1	**1a**	None	26	63:37	50:50	80
2	**1a**	$InCl_3$	1		Mixture of products	
3	**1a**	$In(OTf)_3$	1.5		Mixture of products	
4	**1a**	$MgBr_2$	9	<05:95	ND	91
5	**1a**	$Zn(OTf)_3$	6	78:22	55:45	92
6	**1a**	$Y(OTf)_3$	5	78:22	54:46	90
7	**1a**	$Sm(OTf)_3$	7	72:28	52:48	78
8	**1a**	$Yb(OTf)_3$	2	87:13	55:45	92 (89)[d]
9	**1b**	$Yb(OTf)_3$	0.5	>99:01	58:42	97 (98)

[a] Lewis acid catalyzed halohydroxylation was performed with 1.5 equiv of NBS and 0.15 equiv of metal salts in 5% aqueous CH_3CN at rt (25 °C).
[b] Determined from the ^1H NMR spectrum of the crude reaction mixture; well separated C*H*Br ^1H NMR signals were used to assign the ratio of **2**/**2′** and **3**/**3′** and the dr of **2** and **2′**.
[c] Combined yields of halohydroxy- and dibromo-carbonyl compounds, determined by ^1H NMR analysis of the crude reaction mixture with naphthalene as internal standard. Yields in parenthesis refer to the combined isolated yields of the bromohydroxy- and dibromo-carbonyl compounds.
[d] Isolated yields of the bromohydroxycarbonyl compounds **2a** (42%) and **2a′** (36%) and the dibromocarbonyl compounds **3a**/**3a′** (11%). ND: Not determined.

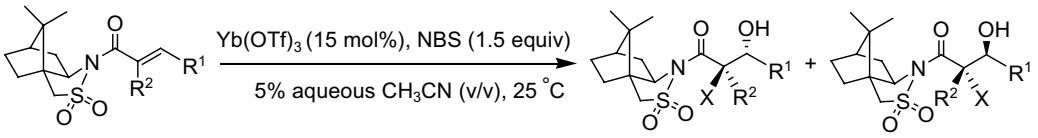
metal halides and acetates, such as $CuCl_2$, $NiCl_2$, $CoCl_2$, $Co(OAc)_2$, $Ni(OAc)_2$ and $Cu(OAc)_2$ did not show any catalytic effect for the halohydroxylation of **1a** with NBS. The metal triflates, such as $Zn(OTf)_2$, $Y(OTf)_3$, $Sm(OTf)_3$ and $Yb(OTf)_3$ as catalysts, showed good results (entries 5–8). Among these, $Yb(OTf)_3$ was found to be the best catalyst for the halohydroxylation of **1a**. When **1a** was treated with NBS (1.5 equiv) in 5% aqueous acetonitrile (v/v) in the presence of the $Yb(OTf)_3$ catalyst (15 mol %) at rt it gave the desired bromohydrins **2a** and **2a′** in good yield within 2 h, along with a minor amount of the dibromocarbonyl compounds **3a**/**3a′** (entry 8).[9,10] Similarly the electron-rich cinnamoyl substrate **1b** underwent clean bromohydroxylation with NBS (1.2 equiv) in the presence of the $Yb(OTf)_3$ catalyst.[11] In this case no dibromocarbonyl compound **3b**/**3b′** was observed (entry 9). However, the diastereoselectivities of the above bromohydroxylations were rather low.

Since the oxazolidinone chiral auxiliary gave low diastereoselectivity for the $Yb(OTf)_3$ catalyzed bromohydroxylation of **1a** and **1b**, we examined the $Yb(OTf)_3$ catalyzed bromohydroxylation of α,β-unsaturated carboxylic acid derivatives possessing Oppolzer's sultam chiral auxiliary.[12] When the $Yb(OTf)_3$ catalyzed bromohydroxylation of (2*R*)-*N*-cinnamoylbornanesultam **4a** was performed under the same reaction conditions, moderate diastereoselectivity was observed with good yields (Table 2; entry 1). This $Yb(OTf)_3$ catalyzed halohydroxylation reaction was further studied using a variety of cinnamoyl substrates containing electron-donating and -withdrawing substituents on the aromatic ring as well as different alkenoyl substrates. It was found that the electron-rich cinnamoyl substrates **4b**, **4c** and *E*-**4g** and the β-(2-naphthyl)enoyl substrate **4h** smoothly underwent bromohydroxylation (entries 2, 3, 7 and 8) under the same reaction conditions.[13] The more electron-rich cinnamoyl substrates **4d**, **4e** and **4f**[14] preferred to undergo iodohydroxylation efficiently with NIS (entries 4–6) and yielded the electrophilic bromination product of the aromatic moiety as the major product with NBS. However, the electron-deficient cinnamoyl substrates **4i** and **4j** did not undergo halohydroxylation under the same reaction conditions, even with the use of excess reagents under different reaction conditions using either NCS, NBS or NIS as the halogen source. The alkenoyl substrates **4k** and **4l** and also the *E*-α-methyl alkenoyl substrate *E*-**4m** responded to the bromohydroxylation with 100% regioselectivity in contrast to the Ag(I)-promoted halohydrin reactions of *N*-alkenoyl-2-oxazolidinone.[6] It is important to note that the substrates **4k**, **4l** and *E*-**4m** did not undergo any halohydroxylation in the absence of Lewis acid.

The pure α-halo-β-hydroxycarbonyl compounds **5** and **6** were fully characterized by ^1H and ^{13}C NMR and elemental (CHN) analysis[13] and their configurational assignments were made by confirming the stereochemistry of the major isomer **5b**. Pure **5b** was transformed to the epoxide **7b** (Scheme 1) and the optical rotation of **7b** ($[\alpha]_D^{22.4}$ +212.2, (*c* 1.0, MeOH)) was compared with the literature data ($[\alpha]_D^{24}$ −205 (*c* 1.0, MeOH)).[15]

β-Methoxy-α-amino acids are unusual amino acid constituents of many biologically active cyclic peptide and depsipeptide antibiotics such as callipeltines,[16] papuamides,[17] cyclomarins[18] and discokiolide.[19] α-Halo-β-methoxycarboxylic acid derivatives are important precursors to β-methoxyamino acids.[6a] The $Yb(OTf)_3$

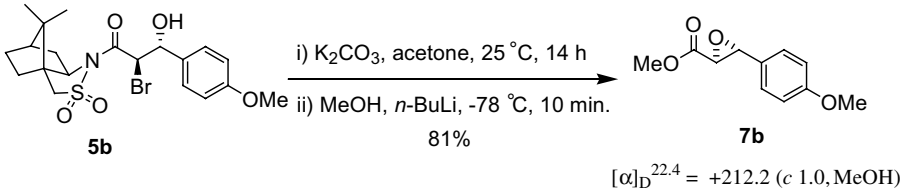
Table 2. $Yb(OTf)_3$ catalyzed halohydroxylation of (2*R*)-*N*-enoylbornanesultams **4**



4 **5** **6**

Entry	Substrate	R^1	R^2	*t* (h)	X	dr[a] (**5**:**6**)	Yield[b](%)
1	**4a**	C_6H_5	H	8	Br	64:36	80 (12)
2	**4b**	4-$MeOC_6H_4$	H	2	Br	72:28	93
3	**4c**	4-$BnOC_6H_4$	H	3	Br	74:26	91
4	**4d**	3,4-$MeOC_6H_3$	H	1.5	I	75:25	94
5	**4e**	4-BnO-3-$MeOC_6H_3$	H	3	I	76:24	90
6	**4f**	3,4,5-$MeOC_6H_2$	H	3	I	78:22	71[c]
7	*E*-**4g**	4-$MeOC_6H_4$	CH_3	6	Br	82:18	95
8	**4h**	2-Naphthyl	H	10	Br	65:35	88
9	**4i**	2-ClC_6H_4	H	48	Cl/Br/I		NR
10	**4j**	2-$NO_2C_6H_4$	H	48	Cl/Br/I		NR
11	**4k**	CH_3	H	36	Br	72:28	78 (20)
12	**4l**	C_6H_{13}	H	36	Br	68:32	81 (10)
13	*E*-**4m**	C_6H_{13}	CH_3	36	Br	70:30	80 (12)

Yields in parentheses refer to the isolated yield of dibromocarbonyl compounds. NR: No reaction.
[a] Determined from the ^1H NMR spectrum of the crude reaction mixture.
[b] Combined isolated yields of pure **5** and **6** after column chromatography.
[c] Isolated yield of isomer **5f**.[14]

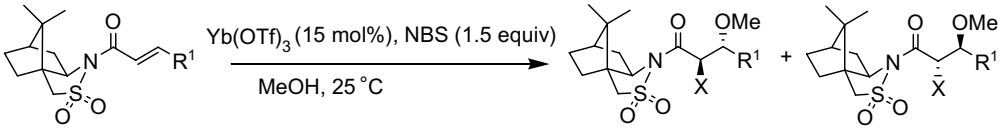


5b **7b**

$[\alpha]_D^{22.4} = +212.2$ (*c* 1.0, MeOH)

Scheme 1.

Table 3. $Yb(OTf)_3$ catalyzed halomethoxylation of **4**



4 **8** **9**

Entry	Substrate	R^1	*t* (h)	X	dr[a] (**8**:**9**)	Yield[b](%)
1	**4a**	C_6H_5	7	Br	65:35	52
2	**4a**	C_6H_5	8	I	67:33	87
3	**4b**	4-$MeOC_6H_4$	3	Br	78:22	98
4	**4c**	4-$BnOC_6H_4$	4	Br	75:25	91
5	**4d**	3, 4-$MeOC_6H_3$	2	I	79:21	97
6	**4e**	4-BnO-3-$MeOC_6H_3$	2	I	75:25	90
7	**4h**	2-Naphthyl	9	Br	63:37	90
8	**4i**	2-ClC_6H_4	48	Cl/Br/I		NR
9	**4j**	2-$NO_2C_6H_4$	48	Cl/Br/I		NR
10	**4k**	CH_3	24	Br	66:34	71 (10)
11	**4l**	C_6H_{13}	24	Br	62:38	78 (8)

Yields in parentheses refer to the dibromocarbonyl compounds. NR: No reaction.
[a] Determined from the ^1H NMR spectrum of the crude reaction mixture.
[b] Combined isolated yields of pure **8** and **9** after column chromatography.

catalyzed asymmetric halohydrination, therefore, was further applied to the catalytic asymmetric halomethoxylation of different (2*R*)-*N*-enoylbornanesultam substrates **4** (Table 3). It was found that when a methanolic

solution of substrate **4a** was treated with NBS (1.5 equiv) in the presence of the $Yb(OTf)_3$ catalyst (15 mol %) at rt, it gave the desired bromomethoxycarbonyl compounds in 52% yield (entry 1). The iodomethoxylation of **4a** under the same reaction conditions using NIS instead of NBS provided the iodomethoxycarbonyl compounds in 87% yield with moderate diastereoselectivity (entry 2). The stereochemistry of the major isomer **8a** was assigned by analogy with the above halohydroxylation reactions. The compound **8a** could easily be transformed into the *N*-protected *syn*-β-methoxyphenylalanine, the unusual amino acid component of cyclomarins.[14,6a] The electron-rich cinnamoyl substrates **4b**, **4c** and the β-(2-naphthyl)enoyl substrate **4h** responded to the bromomethoxylation with moderate to good diastereoselectivities (entries 3, 4 and 7) and the more electron-rich cinnamoyl substrates **4d** and **4e** preferred to undergo iodomethoxylation with NIS (entries 5 and 6). Similar to the halohydroxylation, the electron-deficient cinnamoyl substrates **4i** and **4j** did not undergo any halomethoxylation even under more vigorous reaction conditions. We also studied the halomethoxylation of alkenoyl substrates **4k** and **4l** under the same reaction conditions, which showed 100% regioselectivity, with moderate diastereoselectivity, in good yields.

In summary, we have developed a Lewis acid catalyzed asymmetric halohydrination, (halohydroxylation as well as halomethoxylation) of chiral α,β-unsaturated carbonyl compounds with NXS (X = Br, I) as the halogen source. Regio- and *anti*-selectivity of 100% and moderate to good diastereoselectivity with good yields was observed when bornanesultam was used as the chiral auxiliary. Most of the metal halides and acetates did not catalyze the halohydrin reactions, but metal triflates showed good catalytic activity for the halohydrination of α,β-unsaturated carbonyl compounds. Among the metal triflates, $Yb(OTf)_3$ was found to be the best catalyst. Alkenoyl, cinnamoyl and moderately electron-rich cinnamoyl substrates smoothly underwent the $Yb(OTf)_3$ catalyzed bromohydrin reactions with NBS whilst the more electron-rich cinnamoyl substrates preferred to undergo iodohydrin reactions with NIS. The cinnamoyl substrates possessing electron-withdrawing substituents on the aromatic ring did not respond to the Lewis acid catalyzed halohydrin reaction with either NCS, NBS or NIS. This methodology offers an alternative method for the synthesis of chiral α-halo-β-hydroxy/methoxy carboxylic acid derivatives using easily available *N*-halosuccinimide as the halogen source. A better understanding of Lewis acid catalyzed halohydrin reactions may provide a catalytic and enantioselective method for the halohydrination of olefins. We are currently attempting to improve the diastereoselectivity of this process and we are applying this concept to other catalytic 1,2-halo functionalizations of olefins.

Acknowledgements

We thank DST, New Delhi and CSIR, New Delhi for providing financial support. M.B. thanks IIT, Kharagpur and A.K. thanks CSIR, New Delhi for their fellowships.

References and notes

1. (a) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W.A. Benjamin: Menlo Park, CA, 1972, p 432; (b) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992, 815; (c) Carey, F.; Sundberg, R. *Advanced Organic Chemistry, Part B*, 4th ed.; Plenum: New York, 2001, p 203.
2. *Ullmann's Encyclopedia of Industrial Chemistry*, 6th ed.; Electronic Release, 1998 Cabanal-Duvillard, I.; Berrier, J. F.; Royer, J.; Husson, H. P. *Tetrahedron Lett.* **1998**, *39*, 5181.
3. (a) El-Qisairi, A.; Hamed, O.; Henry, P. M. *J. Org. Chem.* **1998**, *63*, 2790; (b) Dewkar, G. K.; Srinivasarao, V. N.; Sudalai, A. *Org. Lett.* **2003**, *5*, 4501; (c) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon: Oxford, 1991; Vol. 4, pp 344–347.
4. (a) Ohno, M.; Otsuka, M. In *Recent Progress in Chemical Synthesis of Antibiotics*; Lukas, G., Ohno, M., Eds.; Springer: New York, 1990; (b) Dong, L.; Miller, M. J. *J. Org. Chem.* **2002**, *67*, 4759; (c) Evans, D. A.; Ellman, J. A.; De Vries, K. M. *J. Am. Chem. Soc.* **1989**, *111*, 8912; (d) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151; (e) Tseng, T. C.; Wu, M. J. *Tetrahedron: Asymmetry* **1995**, *6*, 1633; (f) Nicolaou, K. C.; Kataoka, T. C.; Caulfield, T.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 7910; (g) Sheehan, J. C.; Mania, D.; Nakamura, S.; Stock, J. A.; Maeda, K. *J. Am. Chem. Soc.* **1968**, *90*, 462; (h) Boger, D. L.; Memezes, R. F. *J. Org. Chem.* **1992**, *57*, 4331.
5. (a) Ishihara, T.; Mima, K.; Konno, T.; Yamanaka, H. *Tetrahedron Lett.* **2002**, *43*, 3493; (b) Guindon, Y.; Rancourt, J. *J. Org. Chem.* **1998**, *63*, 6554; (c) Nagano, H.; Kuno, Y.; Omori, Y.; Iguchi, M. *J. Chem. Soc., Perkin. Trans. 1* **1996**, 389; (d) Hart, D. J.; Krishnamurthy, R. *J. Org. Chem.* **1992**, *57*, 4457.
6. (a) Hajra, S.; Karmakar, A. *Tetrahedron Lett.* **2004**, *45*, 3185; (b) Hajra, S.; Karmakar, A.; Bhowmick, M. *Tetrahedron* **2005**, *61*, 2279.
7. Smietna, M.; Gouverneur, V. *Mioskowski Tetrahedron Lett.* **2000**, *41*, 193.
8. (a) McKennon, M. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 3568; (b) Evans, D. A.; Mathre, D. J.; Scott, W. L. *J. Org. Chem.* **1985**, *50*, 1830; (c) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290.
9. Pure compounds **2a** and **2a′** were fully characterized and their stereochemistry was assigned in our earlier report.[6b]
10. The dr of **3a/3a′** was also the same as for the halohydrins. It was determined by ^{13}C NMR spectral analysis because no separated ^1H NMR signal was found for the diastereomers of dibromocarbonyl compound **3a/3a′** in the ^1H NMR spectrum in $CDCl_3$.
11. Representative spectral data of **2b**: ^1H NMR (200 MHz, $CDCl_3$) δ 7.35 (d, J = 6.6 Hz, 2H), 6.90 (d, J = 6.7 Hz, 2H), 5.88 (d, J = 8.3 Hz, 1H), 5.13 (d, J = 8.3 Hz, 1H), 4.49–4.45 (m, 1H), 4.28–4.23 (m, 2H), 3.80 (s, 3H), 2.71–2.25 (m, 2H), 0.93 (d, J = 7.0 Hz, 3H), 0.92 (d,J = 7.0 Hz, 3H);^{13}C NMR (50 MHz, $CDCl_3$) δ 168.9, 159.6, 153.0, 131.3, 128.4, 113.7, 74.2, 63.5, 58.3, 55.1, 45.1, 28.0, 17.6, 14.7. **2b′**: ^1H NMR (200 MHz, $CDCl_3$) δ 7.36 (d, J = 6.7 Hz, 2H), 6.90 (d, J = 6.7 Hz, 2H), 6.00 (d, J = 7.5 Hz, 1H), 5.10 (d, J = 7.7 Hz, 1H), 4.52–4.39 (m, 1H), 4.26–4.17 (m, 2H), 3.80 (s, 3H), 2.45–2.20 (m, 1H), 0.89 (d,

J = 6.9 Hz, 3H), 0.71 (d, J = 6.9 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.2, 159.6, 153.1, 131.3, 128.1, 113.8, 75.0, 63.4, 58.9, 55.1, 44.6, 28.2, 17.7, 14.3.

12. Vandewall, M.; Van der Eycken, J.; Oppolzer, W.; Uullioud, C. *Tetrahedron* **1986**, *42*, 4035.
13. Diastereomers of halohydrins **5** and **6** were isolated in pure form and fully characterized by ^{1}H and ^{13}C NMR and elemental (CHN) analysis. Representative spectral data for **5b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35 (d, J = 6.3 Hz, 2H), 6.90 (d, J = 6.7 Hz, 2H), 5.11 (d, J = 8.1 Hz, 1H), 5.05–4.92 (br d, J = 8.0 Hz, 1H), 4.05–3.88 (m, 1H), 3.80 (s, 3H), 3.50 (d, J = 4.6 Hz, 2H), 2.28–2.00 (m, 3H) 2.00–1.25 (m, 4H), 1.17 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.7, 159.6, 130.9, 128.2, 113.7, 74.5, 64.7, 55.0, 52.7, 48.6, 47.7, 46.5, 44.3, 37.4, 32.5, 26.2, 20.5, 19.7. Anal. Calcd for $C_{20}H_{26}BrNO_5S$: C, 50.85; H, 5.55; N, 2.97%. Found: C, 51.18; H, 5.61; N, 2.66%. **6b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 5.07 (quasi q, J = 2.8 Hz, 2H), 3.82 (m, 1H), 3.79 (s, 3H), 3.45 (s, 2H), 2.20–1.75 (m, 5H), 1.75–1.10 (m, 3H), 0.91 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.2, 159.6, 130.9, 127.7, 113.7, 75.9, 65.2, 55.1, 52.6, 48.3, 47.5, 46.3, 44.4, 37.7, 32.6, 26.1, 20.1, 19.6. Anal. Calcd for $C_{20}H_{26}BrNO_5S$: C, 50.85; H, 5.55; N, 2.97%. Found: C, 51.14; H, 5.20; N, 2.83%.
14. The minor isomer **6f**, from the iodohydroxylation of **4f**, could not be obtained in pure form due to its instability during silica gel column chromatography.
15. Furutani, T.; Imashiro, R.; Hatsuda, M.; Seki, M. *J. Org. Chem.* **2002**, *67*, 4599.
16. (a) Zampella, A.; D'Auria, M. V.; Paloma, L. G.; Casapula, A.; Minale, L.; Debitus, C.; Henin, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6202; (b) Zampella, A.; Randazzo, A.; Borbone, N.; Luciani, S.; Trevisi, L.; Debitus, C.; D'Auria, M. V. *Tetrahedron Lett.* **2002**, *43*, 6163.
17. Ford, P. W.; Gustafson, K. R.; McKee, T. C.; Shigematsu, N.; Maurizi, L. K.; Pannell, L. K.; Williams, D. E.; Silva, E. D.; Lassota, P.; Allen, T. M.; Soest, R. V.; Andersen, R. J.; Boyd, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 5899.
18. Renner, M. K.; Shen, Y. C.; Cheng, X. C.; Jensen, P. R.; Frankmoelle, W.; Kauffman, C. A.; Fenical, W.; Lobkovsky, E.; Clardy, J. *J. Am. Chem. Soc.* **1999**, *121*, 11273.
19. Haruhiko, T.; Takehiko, T.; Yoshihiro, T.; Fumiaki, H. *Chem. Lett.* **1992**, 431.