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Stieglitz rearrangement of *N,N*-dichloro-β,β-disubstituted taurines under mild aqueous conditions

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ABSTRACT

New topical anti-infectives comprised of *N,N*-dichloro-β,β-disubstituted taurines [*Tetrahedron Lett.* **2008**, *49*, 2193; *Biorg. Med. Chem. Lett.* **2009**, *19*, 196] have been examined for structure–stability relationships (SSR) based upon various alkyl, heteroalkyl and cycloalkyl β-substitutions. These substitutions affect order-of-magnitude changes in the aqueous stability of these *N,N*-dichloroamines which can undergo Stieglitz rearrangement of alkyl groups under extremely mild conditions (H_2O, pH 4–7, 0–20 mM acetate or phosphate buffer, 20–40 °C). This process produces β-ketosulfonic acids which function as substrates for chlorination by the *N*-chlorotaurines which leads to their further degradation.

Halogens and halogenating agents have long been used as disinfectants,[2] antiseptics,[3] and antimicrobials.[4] While effectively killing bacteria,[4] fungi,[4f,5] and viruses,[6] many of these chlorinating agents are also toxic to mammalian cells,[7] which limits their application as therapeutics for sensitive topical applications such as wounds and ocular infections.

In particular, chloramine[8] and organic *N*-chloramines[4f,9] have been used as mild antimicrobials and as CNS drugs.[10] These exhibit lower mammalian cytotoxicity versus chlorine and chloramides while maintaining their antimicrobial activities. In the body, the generation of hypochlorous acid in neutrophils which contain high concentration of taurine[11] leads to *N*-chlorinated taurines.[12] Due to their nonspecific mechanism of action, these compounds have low potential for the development of spontaneous resistance.

While chloroamides are more active at higher pH,[13] the antimicrobial[9a,3a] and chlorinating activity[14] of organic *N*-chloramines increases in mildly acidic solution. Unfortunately, *N*-chloramines readily disproportionate to give amines and *N,N*-dichloramines.[9a,15] Because *N,N*-dichloramines themselves are antimicrobial agents,[4f] it is difficult to separate the contribution to the antimicrobial activity of *N*-chloramines at neutral or acidic pH from the activity of the *N,N*-dichloramines that are generated under these conditions.

The *N,N*-dichloramines, which are the dominant species at the more desirable low pH region,[9a,15] undergo dehydrochlorination if hydrogens are present on the carbon adjacent to the dichloroamine in the molecule.[16] With the β,β-disubstitution of the *N,N*-dichlorotaurines, this decomposition pathway is prevented.[1] We expected that these derivatives would retain their antimicrobial activity and exhibit greater stability than *N,N*-dichlorotaurine or *N*-chlorotaurine. Moreover, this substitution would increase the lipophilicity of the derivatives which is critical for many topical therapeutic agents. In the present study, we report the synthesis of a number of novel β,β-disubstituted *N,N*-dichlorotaurines (**1a–k**) examining their stabilities to assess their suitability as antimicrobial agents (see Fig. 1).

Synthesis of N,N-dichloro-β,β-disubstituted taurines (**1**). The synthesis of β,β-disubstituted taurines (**5**) was accomplished by one of two general synthetic schemes based upon the commercial availability of the required starting materials. In the first approach, we developed a route in which a sulfur atom, either as sulfite[17] or sulfide,[18] opens an aziridine generated *in situ* from a suitably derivatized β,β-disubstituted β-amino alcohol (Scheme 1). These, in turn, are readily prepared by the reduction of the corresponding amino acids. The aminosulfonates **5a–c**, **5f–h**, and **5k** were prepared through this protocol (Table 1).

Our second synthetic approach to **5** involves the nucleophilic addition of ethoxysulfonylmethyl anions to imines to provide the

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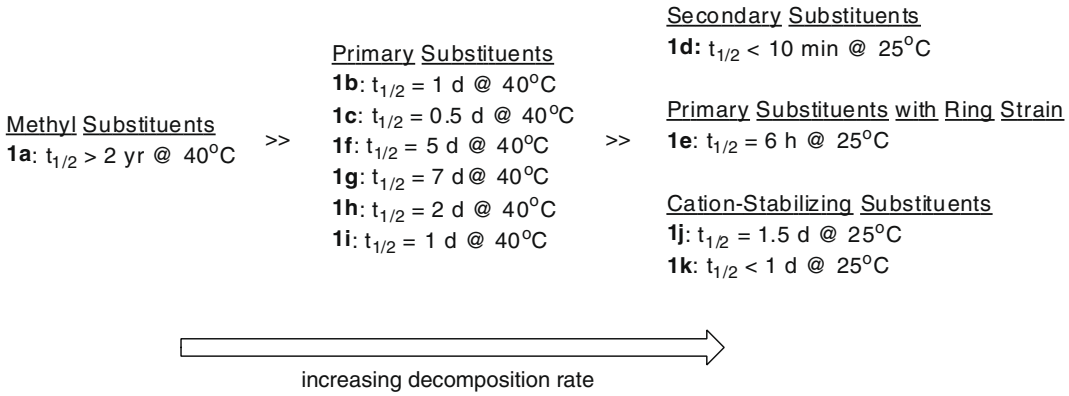
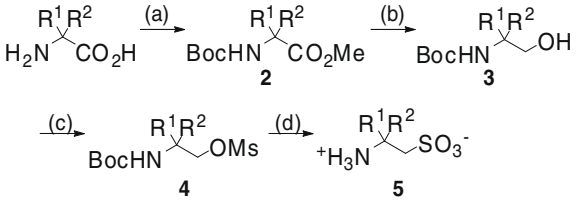
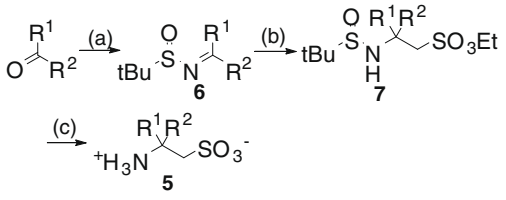


Figure 1. Summary for the relative stabilities of **1**.



Scheme 1. Reagents and conditions: (a) 1—Boc_2O, $NaHCO_3$, THF/H_2O, 0 °C, 2–18 h; 2—$TMSCHN_2$, MeOH/THF, 0–20 °C, 2–4 h; (b) $LiBH_4$, THF/EtOH, 0–20 °C, 18–24 h; (c) MsCl, NEt_3, CH_2Cl_2, 0 °C, 1–3 h; (d) 1—HCl, 1,4-dioxane, 25 °C, 1 h; 2—Na_2SO_3, H_2O, 20–50 °C, 2–18 h.



Scheme 2. Reagents and conditions: (a) *t*-$BuSONH_2$, $Ti(OEt)_4$, 50–70 °C, 2–18 h; (b) $MeSO_3Et$, *n*-BuLi, THF, HMPA, −78 °C, 4 h; (c) 1—LiOH, THF/MeOH/H_2O, 25 °C, 4–18 h; 2—HCl, MeOH, 1,4-dioxane, 25 °C, 15 min.

Table 1
Synthesis of β,β-disubstituted taurines **5**

R^1, R^2	Series	**2** (%)	**3** (%)	**4** (%)	**5** (%)
Me, Me	**a**	NA	90[a]	82	50
Et, Et	**b**	96	86	85	61
Pr, Pr	**c**	56	86	55	41
$(CH_2)_4$	**f**	NA	83[a]	95	93
$(CH_2)_5$	**g**	NA[b]	79[b]	96	71
$(CH_2)_6$	**h**	94	88	65	36
$(CH_2)_2OCH_2$	**k**	42	88	79	32

[a] Yield given for Boc-protection of corresponding amino alcohol (Boc_2O, NEt_3, CH_2Cl_2, 0 °C, 2 h) rather than reduction of methyl ester.
[b] Yield over two steps.

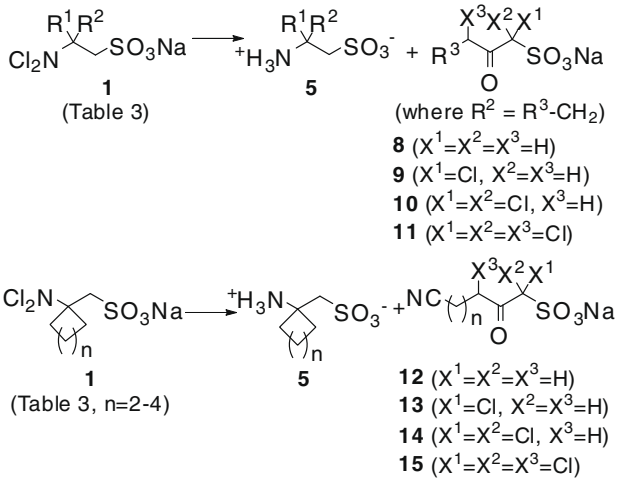
Table 2
Alternative synthesis of β,β-disubstituted taurines **5**

R_1, R_2	Series	**6** (%)	**7** (%)	**5** (%)
Me, Me	**a**	37	21	NA[a]
i-Pr, *i*-Pr	**d**	19	41	35
$(CH_2)_3$	**e**	64	30	NA[a]
$(CH_2CMe_2)_2CH_2$	**i**	78	15	7
Me, CH_2OMe	**j**	26[b]	42[c]	100

[a] Not isolated.
[b] Formed as a 2:1 *E*/*Z* mixture.
[c] Formed as a 2:1 mixture of diastereomers.

β-aminosulfonate skeleton. Anion additions to imines are well-precedented for carbanions,[19] cyanide,[20] enolates,[21] diethylmethylphosphonate anions,[22] fluorosulfonate,[23] and phenylsulfonyl-(difluoro)methyl anions.[24] We reasoned that the addition of ethoxysulfonylmethides to *N*-sulfinyl ketimines would also occur to provide an alternative route to **5** for cases where the amino acid or amino alcohol precursors were either unavailable or prohibitively expensive.

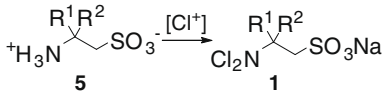
Condensation of a variety of ketones with *tert*-butanesulfinamide under the conditions developed by Ellman provided the corresponding *N*-sulfinyl imines **6**.[25] A variety of bases and co-solvents were screened to find the best conditions for the formation of ethoxysulfonylmethide and its addition to **6a** ($MeSO_3Et$, *n*-BuLi, THF, HMPA, −78 °C, 4 h). While the results for the optimization were disappointing, these conditions did provide an alternative entry to **5** which was employed for the synthesis of several β,β-disubstituted taurines **5** (Scheme 2 and Table 2). The intermediate adducts **7** were hydrolyzed, first under basic conditions and the sulfinyl protecting group removed with acidic methanol to give the corresponding β-aminosulfonates **5a**, **5d**–**e**, and **5i**–**j**. (Scheme 3).



Scheme 3.

The *N*-chlorinations of **5** were performed using one of three methods: **A** (trichloroisocyanuric acid (TCI) in water), **B** (HOCl, prepared in situ by the acidification with 6 M HCl of commercial

Table 3
Compound **1** from the chlorination of **5**



Series	R^1, R^2	Method[a]	**1** (%)
a	Me, Me	**A**	28
b	Et, Et	**C**	76[b]
c	Pr, Pr	**B**	60
d	*i*-Pr, *i*-Pr	**B**	NA[c]
e	$(CH_2)_3$	**B**	NA[c]
f	$(CH_2)_4$	**B**	34
g	$(CH_2)_5$	**A**	24
h	$(CH_2)_6$	**C**	43[b]
i	$(CH_2CMe_2)_2CH_2$	**C**	51[b]
j	Me, CH_2OMe	**B**	61
k	$(CH_2)_2OCH_2$	**B**	NA[c]

[a] **A** (trichloroisocyanuric acid (TCI) in water), **B** (HOCl, prepared in situ by the acidification with 6 M HCl of commercial bleach to pH 4–5), or **C** (*t*-BuOCl in methanol).
[b] Chlorination by *tert*-butylhypochlorite gives the sulfonic acid.
[c] Unstable compound, not isolated in pure form.

Table 4
Summary of stability data for **1**

Compound	Conditions	$t_{1/2}$
1a	pH 4, 40 °C	>2 y
1b	pH 4, 40 °C	1 d
1b	pH 7 buffer, 40 °C	0.5 d
1c	pH 4, 40 °C	0.5 d
1c	pH 7 buffer, 40 °C	2 d
1d	pH 4, 25 °C	<10 min
1e	pH 4, 25 °C	6 h
1f	pH 4 buffer, 40 °C	5 d
1f	pH 7 buffer, 40 °C	1 d
1g	pH 4 buffer, 40 °C	7 d
1h	pH 4 buffer, 40 °C	2 d
1i	pH 4, 40 °C	1 d
1j	pH 4, 25 °C	1.5 d
1k	pH 4, 25 °C	<1 d

bleach to pH 4–5), or **C** (*t*-BuOCl in methanol). The resulting *N*,*N*-dichlorotaurines **1** appear to be stable to either silica gel chromatography or preparative-scale reverse-phase HPLC. Compounds **1a**–**1c** and **1f**–**1j** were stored as purified powders for several months at −20 °C. However, the inherent instability of the other derivatives prevented their isolation in pure form and their characterization could only be accomplished through LC–MS (Table 3).

Results and discussion. Solution stabilities of 1–4 mM compounds **1a**–**1k** were evaluated at a variety of pH values (4–7) and buffer concentrations (4–20 mM). The samples were incubated at 25 or 40 °C and quantified either by the UV signature of the dichloroamine chromophore ($A_{300-310}$) or by HPLC (Table 4).

Surprisingly, the stabilities of **1** varied by several orders of magnitude for the examples studied. Thus, some decomposed at room temperature in minutes, while others were stable for years at elevated temperatures. Since only small differences were found for compounds at different pH values and buffers, the large variations in stabilities with seemingly small structural changes were puzzling.

Fully degraded samples were analyzed by LC–MS (see Supporting Information) employing a H_2O/MeOH gradient. Detection and analysis was performed by ELSD and MS (ESI-APCI dual ionization, negative mode). These data are presented in Table 5. The degradation products were identified by MS and NMR as either de-*N*-chlorinated taurines **5** or β-ketoalkanesulfonates (**8** or **12**) which we view as arising from a Stieglitz rearrangement,[26] together with their chlorinated derivatives. (Scheme 3). Stieglitz rearrangements have been reported in organic solvents for aryl and stabilized alkyl migrating groups, but not under mild aqueous conditions with unstabilized alkyl groups.[27]

Several aspects of the data presented in Table 5 warrant further discussion. As noted above, the de-*N*-chlorinated taurines **5** were always observed in the decomposition process. The β-ketosulfonates were also observed together with their chlorinated counterparts which each successively increasing by 34 mass units corresponding to the replacement of one hydrogen atom with a chlorine atom. The characteristic isotopic distributions for one, two or three chlorine atoms are observed in the MS of each of these products. In the acyclic cases, the β-ketosulfonates **8** are lower in mass than **5**, while in the cyclic cases, these β-ketosulfonates **12** are higher in mass than their taurine counterparts **5**. Moreover, in the acyclic cases, the β-ketosulfonates have masses which are a different odd–even parity than **5** consistent with the loss of a nitrogen atom. Also, by comparing the diethyl and dipropyl derivatives, we can observe that the difference in mass between the degradants **8** is only 14 amu (1× CH_2), while the difference between the **5b** and **5c** is 28 amu (2× CH_2) indicating that only one side chain is retained in **8**. This data is wholly consistent with the assigned structures.

Through preparative-scale HPLC, analytically pure fractions of many of these decomposition products (see Table 5) were isolated and ^{1}H NMR was employed to confirm the assigned structures (D_2O, 400 MHz).

Proposed mechanism. Our proposed mechanism is shown in Scheme 4. It involves an initial Stieglitz rearrangement of the alkyl and cycloalkyl derivatives to generate an intermediate *N*-chloroiminium species, which is readily hydrolyzed to the ketone and the *N*-chloroalkylamine (Scheme 4). Acyclic derivatives produce **8** (Scheme 4a). However, the formation of the nitrile moiety in **12f**–**h** from the cyclic derivatives **1f**–**h** suggests that the corresponding hydrolysis of **A** giving **B** may be reversible, stabilizing **B** until it is further chlorinated to **C** through transchlorination (Scheme 4b). The double dehydrochlorination of **C** could then provide the observed nitrile **12**. Any free imine originating from the dehydrochlorination of **B** would be expected to be readily hydrolyzed to the corresponding aldehyde which was not observed. Chlorination of the enolic forms of the β-ketosulfonates leads to the observed mono- (**9b**–**c**, **13f**–**h**), di- (**10b**–**c**, **14f**–**h**) and trichloro- (**11b**–**c**, **15f**–**h**) derivatives (Scheme 4c).

Previous studies on the migratory aptitudes for the Lewis acid-mediated Stieglitz rearrangement support the assertion that the instability of a compound should be proportional to the cation-stabilizing ability of the migrating side chain.[28] This is wholly consistent with our observations in that there are dramatic differences in the stabilities of **1** which follow the order Me > 1° > 2° for the β-alkyl substituents.

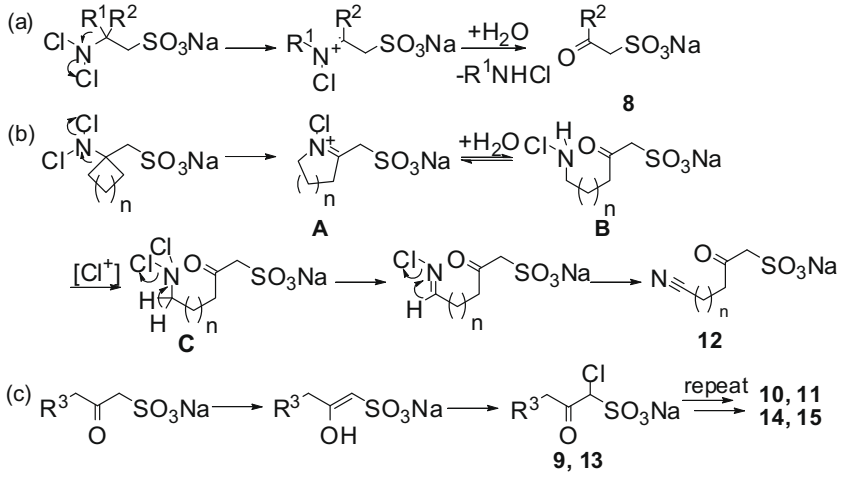
Derivatives **1j** and **1k**, which contain a γ-oxygen capable of stabilizing a cation at the β-position, also show accelerated decomposition relative to their respective non-oxygenated counterparts, **1c** and **1f**. The mechanistic pathways proposed are also consistent with the observed accelerated rate of decomposition of **1e**, which undergoes the Stieglitz rearrangement to relieve ring strain, forming the corresponding *N*-chloro cyclic iminium ions (see Scheme 5). These intermediates can hydrolyze and be further chlorinated with dehydrochlorination providing nitrile derivatives of the β-ketosulfonates (e.g., **12**).

The decomposition of two other cycloalkyl derivatives, **1e** (cyclobutyl) and **1i** (tetramethylcyclohexyl), did not follow the expected pathway, but rather led to products consistent with ω-amino-β-ketosufonates **16** and cyclic imines **17**, which are chlorinated products corresponding to intermediates **A** and **B** in Scheme 4b (in addition to **5e** and **5i**). While it is not definitively known why the

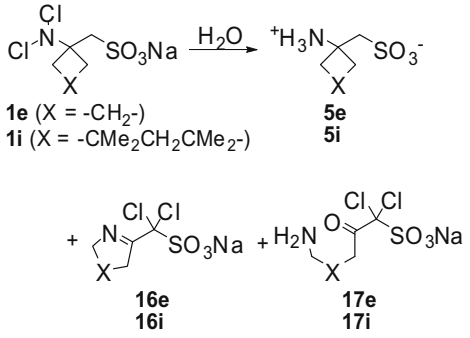
Table 5
Analysis of degraded samples of **1**[a]

Parent compound	**1b** $R^1 = R^2 =$ Et	**1c** $R^1 = R^2 =$ Pr	**1f** $R^1, R^2 = (CH_2)_4$	**1g** $R^1, R^2 = (CH_2)_5$	**1h** $R^1, R^2 = (CH_2)_6$
Degradants	**8b** *1.0* (*151*)	**8c** *1.4* (*165*)	—	**12g** *1.4* (*204*)	**12h** *1.9* (*218*)
	5b 1.4 (180)	**9c** *2.3* (*199**)	**5f** 1.2 (178)	**5g** *1.6* (*192*)	**5h** *2.1* (*206*)
	9b 1.5 (185*)	**5c** 2.7 (208)	**13f** 1.6 (224*)	**13g** *1.9* (*238**)	**13h** 2.5 (252*)
	10b *2.5* (*219***)	**10c** *3.2* (*233***)	**14f** 2.2 (258**)	**14g** *2.6* (*272***)	**14h** *3.1* (*286***)
	11b *3.3* (*253****)	**11c** *3.7* (*267****)	**15f** 2.7 (292***)	—	**15h** 3.8 (320***)

[a] Degradants (bold), with their ELSD retention times (min) and mass-to-charge ratios (in parentheses). Asterisks (*) indicate the presence of chlorine(s) as evidenced by the isotopic ratio in the mass spectrum (e.g., 200* indicates a 3:1 ratio of *m*/*z* 200 to *m*/*z* 202, while 286** indicates a 9:6:1 ratio of *m*/*z* 286 to *m*/*z* 288 to *m*/*z* 290). Italicized entries were isolated by preparative-scale HPLC.



Scheme 4.



Scheme 5.

ω-amines are not oxidized to the corresponding nitriles, we hypothesize that the equilibrium between **A** and **B** is shifted in favor of the cyclic imines in some cases. Evidence for the precise mechanism by which these products are formed is underway and will be disclosed in a separate report.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.12.109.

References and notes

1. (a) Wang, L.; Khosrovi, B.; Najafi, M. R. *Tetrahedron Lett.* **2008**, *49*, 2193; (b) Low, E.; Nair, S.; Shiau, T.; Belisle, B.; Debabov, D.; Celeri, C.; Zuck, M.; Najafi, R.; Georgopapadakou, N.; Jain, R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 196.
2. (a) Worley, S. D.; Sung, G.; Sun, W.; Chen, T. Y. U.S. Patent No. 6,020,491.; (b) Williams, D. E.; Elder, E. D.; Worley, S. D. *Appl. Environ. Microb.* **1988**, *54*, 2583; (c) Connell, G. F. *The Chlorination/Chloramination Handbook*, 1996, American Water Works Association, pp 37–38.; (d) Hussain, A. A.; Tashtoush, B.; Wittert, L. W. U.S. Patent 5985239.; (e) Tilstam, U.; Weinmann, H. *Org. Proc. Res. Dev.* **2002**, *6*, 384.
3. (a) Marcinkiewicz, J.; Biedron, R.; Bialecka, A.; Kasprowicz, A.; Mak, M.; Targosz, M. *Arch. Immunol. Ther. Exp.* **2006**, *54*, 61; (b) Selk, S. H.; Pogany, S. A.; Higuchi, T. *Appl. Environ. Microb.* **1982**, *43*, 899.
4. (a) Kaminski, J. J.; Bodor, N. S. U.S. Patent No. 3,931,213.; (b) Day, D. F. U.S. Patent No. 6,866,870.; (c) Ogata, N. *Biochemistry* **2007**, *46*, 4898; (d) Wang, L.; Bassiri, M.; Najafi, R.; Najafi, K.; Yang, J.; Khosrovi, B.; Hwong, W.; Barati, E.; Belisle, B.; Celeri, C.; Robson, M. C. *J. Burns Wounds* **2007**, *6*, 65; (e) Robson, M. C.; Payne, W. G.; Ko, F.; Mentis, M.; Shafii, S. M.; Culverhouse, S.; Wang, L.; Khosrovi, B.; Najafi, R.; Cooper, D.; Bassiri, M. *J. Burns Wounds* **2007**, *6*, 80; (f) Pogany, S. A.; Higuchi, T. U.S. Patent No. 4,386,103.
5. Nagl, M.; Lass-Florl, C.; Neher, A.; Gunkel, A.; Gottardi, W. *J. Antimicrob. Chem.* **2001**, *47*, 871.
6. (a) McDonnell, G.; Russell, A. D. *Clin. Microb. Rev.* **1999**, *12*(1), 147; (b) Nagl, M.; Larcher, C.; Gottardi, W. *Antiviral Res.* **1998**, *38*, 25; (c) Romanowski, E. G.; Yates, K. A.; Teuchner, B.; Nagl, M.; Irschick, E. U.; Gordon, Y. J. *Invest. Ophthalmol. Vis. Sci.* **2006**, *47*, 2021.
7. (a) Schraufstatter, I. U.; Browne, K.; Harris, A.; Hysiop, P. A.; Jackson, J. H.; Quehenberger, O.; Cochrane, C. G. *J. Clin. Invest.* **1990**, *85*, 554; (b) Cantin, A. M. *J. Clin. Invest.* **1994**, *93*, 606.
8. Connell, G. F. *The Chlorination/Chloramination Handbook*, 1996 American Water Works Association, p 44.
9. (a) Thomas, E. L.; Grisham, M. B.; Jefferson, M. M. Methods in Enzymology; Vol. 132. Springer: Berlin, 1986; pp 569-585.; (b) Cunningham, C.; Tipton, K. F.; Dixon, H. B. F. *Biochem. J.* **1998**, *330*, 939–945; (c) Gottardi, W.; Nagl, M. *J. Antimicrob. Chem.* **2005**, *55*, 475–482; (d) Gottardi, W.; Hagleitner, M.; Nagl, M. *Arch. Pharm. Chem. Life Sci.* **2005**, *338*, 473–483; (e) Gottardi, W.; Nagl, M. *Arch. Pharm. Pharm. Med. Chem.* **2002**, *9*, 411–421.
10. van Gelder, N. M.; Bowers, R. J. U.S. Patent No. 6,451,761.
11. Grisham, M. B.; Jefferson, M. M.; Melton, D. F.; Thomas, E. L. *J. Biol. Chem.* **1984**, *259*, 10404.
12. (a) Weiss, S. J.; Klein, R.; Slivka, A.; Wei, M. *J. Clin. Invest.* **1982**, *70*, 598; (b) Nightingale, Z. D.; Lancha, A. H.; Handelman, S. K.; Dolnikowski, G. G.; Busse, S. C.; Dratz, E. A.; Blumberg, J. B.; Handelman, G. J. *Free Radic. Biol. Med.* **2000**, *29*,

425; (c) Li, J. X.; Pang, Y. Z.; Tang, C. S.; Li, Z. Q. *World J. Gastroenterol.* **2004**, *10*, 694; (d) Nagl, M.; Hess, M. W.; Pfaller, K.; Hengster, P.; Gottardi, W. *Antimicrob. Agents Chem.* **2000**, *44*, 2507.
13. Williams, D. E.; Worley, S. D.; Wheatley, W. B.; Swango, L. J. *Appl. Environ. Microb.* **1985**, *49*, 637.
14. Calvo, P.; Crugeiras, J.; Rıos, A.; Rıos, M. A. *J. Org. Chem.* **2007**, *72*, 3171.
15. Kovacic, P.; Lowery, M. K.; Field, K. W. *Chem. Rev.* **1970**, *70*, 639.
16. (a) Ramachandran, M. S.; Easwaramoorthy, D.; Vasanthkumar, S. *J. Org. Chem.* **1996**, *61*, 4336; (b) Coker, M. S. A.; Hu, W.; Senthilmohan, S. T.; Kettle, A. J. *Chem. Res. Toxicol.* **2008**, *21*, 2334.
17. Braghiroli, D.; Di Bella, M. *Tetrahedron Lett.* **1996**, *37*, 7319.
18. Koller, W.; Linkies, A.; Rehling, H.; Reuschling, D. *Tetrahedron Lett.* **1983**, *24*, 2131.
19. (a) McMahon, J. P.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 1645; (b) Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268.
20. Wang, H.; Zhao, X.; Li, Y.; Lu, L. *Org. Lett.* **2006**, *8*, 1379.
21. (a) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **2002**, *67*, 7819; (b) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12.
22. (a) Mikolajczyk, M.; Lyzwa, P.; Drabowicz, J.; Wieczorek, M. W.; Blaszczyk, J. *Chem. Commun.* **1996**, 1503; (b) Davis, F. A.; Lee, S.; Yan, H.; Titus, D. D. *Org. Lett.* **2001**, *3*, 1757; (c) Roschenthaler, G. V.; Kukhar, V. P.; Belik, M. Y.; Mazurenko, K. I.; Sorochinsky, A. E. *Tetrahedron* **2006**, *62*, 9902.
23. Liu, J.; Zhang, L.; Hu, J. *Org. Lett.* **2008**, *10*, 5377.
24. Liu, J.; Li, Y.; Hu, J. *J. Org. Chem.* **2007**, *72*, 3119.
25. Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278.
26. Stieglitz, J.; Leech, P. N. *J. Am. Chem. Soc.* **1914**, *36*, 272.
27. (a) Ruchenko, V. F.; Shtamburg, V. G.; Pleshkova, A. P.; Kostyanovskii, R. G. *Izv. Akad. Nauk SSSR* **1981**, *5*, 1065; (b) Theodorou, V.; Skobridis, K. *Tetrahedron Lett.* **2005**, *46*, 5021; (c) Theodorou, V.; Skobridis, K.; Karkatsoulis, A. *Tetrahedron* **2007**, *63*, 4284; (d) Rudchenko, V. F.; Kostyanovsky, R. G. *Russ. Chem. Rev.* **1998**, *67*, 179.
28. (a) Kling, T. A.; White, R. E.; Kovacic, P. *J. Am. Chem. Soc.* **1972**, *94*, 7416; (b) Newman, M. S.; Hay, P. M. *J. Am. Chem. Soc.* **1953**, *75*, 2322; (c) Hoffman, R. V.; Poelker, D. J. *J. Org. Chem.* **1979**, *44*, 2364.