COMMUNICATION

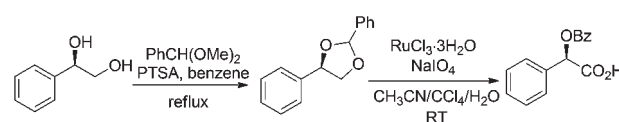# A chemoselective oxidation of monosubstituted ethylene glycol: facile synthesis of optically active α-hydroxy acids†

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A mild and efficient method for the synthesis of optically active α-hydroxy acids through chemoselective oxidation of monosubstituted ethylene glycols using the TEMPO–NaOCl reagent system is described. It is evident from our studies that the solvent, pH and reaction temperature are very crucial for the success of this oxidation. The versatility of this method has been demonstrated with a variety of aliphatic, aromatic and carbohydrate substrates bearing various functional groups.

Introduction

An optically active α-hydroxy acid functional group is one of the most important structural sub-units present in various biologically active natural products and pharmaceutically important molecules.[1] Especially, enantiomerically pure α-hydroxy acids serve as the key building blocks in synthesizing various biologically important complex molecules such as prostaglandins,[2] angiotensin converting enzyme (ACE) inhibitors,[3] semi-synthetic penicillins,[4] cephalosporins,[5] antitumor[6] and anti-obesity agents[7] as well as fine chemicals.[1] Moreover, α-hydroxy acids have found widespread applications in organic synthesis as chiral intermediates,[8] chiral ligands,[9] resolving agents in chiral resolution processes[10] and also as anti-aging factors in the cosmetics industry.[11]

As a result of the wide-ranging applications of α-hydroxy acids in biology as well as in synthetic organic chemistry, considerable efforts towards its synthesis have already been made and, consequently, numerous enzymatic and chemical methods have been reported in the literature.[12–15] The most frequently used synthetic methods include kinetic and enzymatic resolution of racemic α-hydroxy esters,[12] hydrolysis of

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†Electronic supplementary information (ESI) available: Representative experimental procedure and characterization of reaction products. See DOI: 10.1039/c4ob00601a

Scheme 1 Synthesis of chiral α-benzoyloxy carboxylic acids from benzylidene acetals.

cyanohydrin,[13] reduction of prochiral α-ketoesters[14] and stereoselective α-hydroxylation of enolates with oxaziridines.[15] However, many of these methods suffer from low yield and poor stereo- and enantioselectivity.

Very recently, we reported a novel method for the one-pot synthesis of α- and β-benzoyloxy carboxylic acids through regioselective oxidative cleavage of benzylidene acetals using the $RuCl_3$–$NaIO_4$ reagent system (Scheme 1). Further, this methodology was readily extended to the synthesis of optically active α-benzoyloxy carboxylic acids starting from terminal olefins.[16]
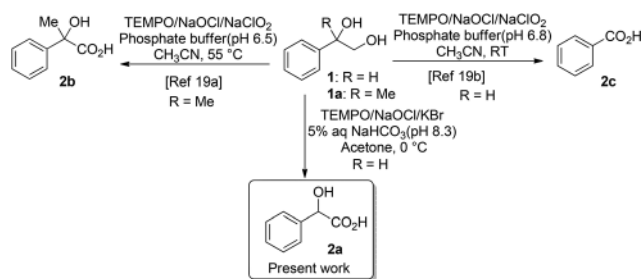
Although several reagent systems, such as $Co(II)$–O_2,[17a–c] PCC,[17d] ruthenium pyrochlore oxides–O_2,[17e] $MoO_2(acac)_2$–^tBuOOH,[17f] WO_4^{2-}–PO_4^{3-}–H_2O_2,[17g] and $TPAP$–NMO,[17h] have been introduced in the literature for the oxidative cleavage of vicinal diols to carboxylic acids, the direct oxidation of vicinal diol to the corresponding α-hydroxy acid has not been fully explored.

Among the various oxidation methods reported till date, TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, free radical) mediated oxidation is generally found to be a mild and highly efficient method for the direct oxidation of primary alcohol to the corresponding carboxylic acid.[18] Massanet *et al.* reported the chemoselective oxidation of 1,1-disubstituted ethylene glycols to the corresponding α-hydroxy acids using the TEMPO–NaOCl–NaClO₂ reagent system in acetonitrile (Scheme 2).[19a] However, under these conditions, the mono-substituted ethylene glycols are found to undergo oxidative cleavage leading to carboxylic acids. Very recently, Shibuya *et al.* carried out a mechanistic investigation on the oxidative cleavage of monosubstituted ethylene glycol to the corres-

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Scheme 2 TEMPO mediated oxidation of substituted ethylene glycols.

ponding carboxylic acid using the same reagent system (TEMPO–NaOCl–NaClO$_2$) in acetonitrile at room temperature. Interestingly, this study suggested that the reactive oxoammonium species (TEMPO$^+$Cl$^-$) promotes overoxidation of mono-substituted ethylene glycol to the corresponding α-ketoacid and subsequent oxidative cleavage of this ketoacid by NaClO$_2$.[19b]

The above mechanistic studies coupled with the biological significance of α-hydroxy acids have motivated us to investigate and develop an efficient and reliable method for the conversion of monosubstituted ethylene glycol to the corresponding α-hydroxy acid under mild reaction conditions.

Our primary effort to identify a TEMPO based reagent system for the efficient oxidation of monosubstituted ethylene glycol to α-hydroxy acid has resulted in the systematic investigation of vicinal diol **3** with the TEMPO–NaOCl reagent system under a variety of reaction conditions.[18g–m] After screening the reaction in different solvents and at various temperatures, it was realized that the solvent, pH and reaction temperature play a very critical role in the TEMPO mediated oxidation of vicinal diol and the results obtained are summarized in Table 1. From these studies, it is evident that the oxidation reaction is generally faster in the acetonitrile solvent. At room temperature, the TEMPO–NaOCl reagent system favours

oxidative cleavage more readily in the presence of phosphate buffer (pH 6.8) (Table 1, entries 1 and 5). Intriguingly, using aqueous 5% NaHCO$_3$ solution as a buffer (pH 8.3), a very clean and selective oxidation of vicinal diol **3** to the corresponding α-hydroxy acid **4a** was observed in acetone at 0 °C (Table 1, entry 8). Significantly, under these reaction conditions, the overoxidized products **4b** and **4c** were not observed. From these studies, it is obvious that the TEMPO–NaOCl–NaHCO$_3$ reagent combination in acetone discriminates primary and secondary alcohols and thus chemoselectively oxidizes the primary alcohol to the corresponding carboxylic acid (Table 1, entries 7 and 8).

Moreover, the stability of α-hydroxy acid was further tested under these oxidation conditions and the results are summarized in Table 2. Unlike phosphate buffer in acetonitrile medium (Table 2, entries 1 and 2), in the presence of NaHCO$_3$ buffer, α-hydroxy acid **4a** was found to be stable in acetone at 0 °C (Table 2, entry 3).

Since the synthetic potential of the TEMPO–NaOCl–NaHCO$_3$ reagent combination has not been fully explored, oxidation of a wide variety of monosubstituted ethylene glycols to α-hydroxy acids has been investigated.[20] Consequently, the oxidation of (*R*)-(−)-phenylethylene glycol **1** with TEMPO–NaOCl–NaHCO$_3$ was carried out in acetone at 0 °C (Scheme 3). Intriguingly, the reaction proceeded readily to afford the corresponding α-hydroxy acid **2a** in excellent yield with a high degree of chemoselectivity. It is evident from the literature that the vicinal diols derived from styrene and allyl benzene are susceptible to undergo oxidative cleavage with the TEMPO–NaOCl–NaClO$_2$ reagent system.[19a] Moreover, under the reaction conditions, the α-hydroxy acid **2a** did not suffer any racemization (Table 3, entry 1).

Table 1 Effect of the solvent, buffer and temperature on the TEMPO mediated oxidation of monosubstituted ethylene glycol **3**

Entry	Solvent	Buffer[a]	T (°C)	Time (h)	Product ratio 4a : 4b : 4c
1	Acetonitrile	A	RT	0.45	0 : 1 : 9
2	Acetonitrile	A	0	1.0	5 : 10 : 3
3	Acetonitrile	B	RT	1.25	7 : 3 : 0
4	Acetonitrile	B	0	1.5	4 : 1 : 0
5	Acetone[b]	A	RT	1.5	5 : 1 : 5
6	Acetone[b]	A	0	1.75	5 : 1 : 1
7	Acetone[b]	B	RT	1.5	9 : 0 : 1
8	**Acetone[b]**	**B**	**0**	**2.0**	**1 : 0 : 0**
9	DCM[c]	B	0	1.25	11 : 1 : 2

[a] A refers to phosphate buffer (pH 6.8) whereas B refers to 5% aq. NaHCO$_3$ buffer (pH 8.3). [b] 0.1 eq. of KBr was used. [c] 0.1 eq. of Bu$_4$NBr was used.

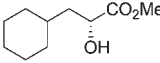**Table 2** Effect of the solvent and temperature on the TEMPO mediated oxidative cleavage of α-hydroxy acid **4a**
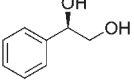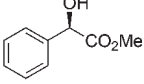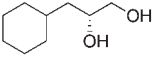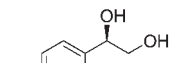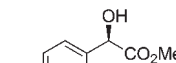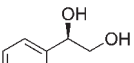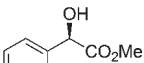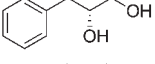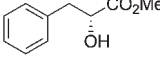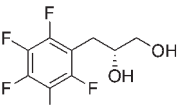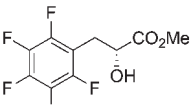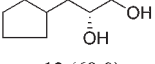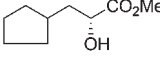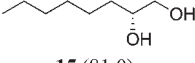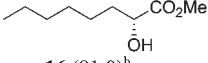
Entry	Solvent	Temperature (°C)	Time (h)	Ratio 4a : 4b : 4c
1	Acetonitrile[a]	0	0.75	0 : 1 : 10
2	Acetonitrile[a]	RT	0.5	0 : 0 : 1
3	Acetone[b]	0	2.0	1 : 0 : 0
4	Acetone[b]	RT	2.0	4 : 0 : 1

[a] Phosphate buffer (6.8 pH) was used. [b] 5% aq. NaHCO$_3$ and 0.1 eq. of KBr were used.
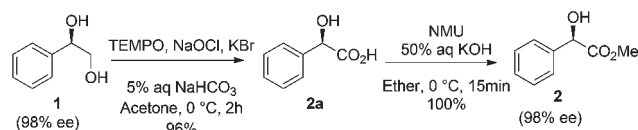
Scheme 3 TEMPO mediated oxidation of monosubstituted ethylene glycol to α-hydroxy acid.

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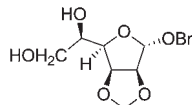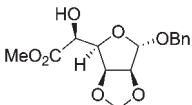
Table 3 Chemoselective oxidation of monosubstituted ethylene glycols to α-hydroxy acids

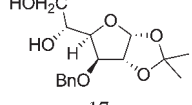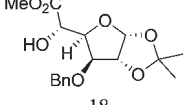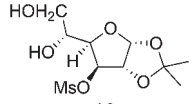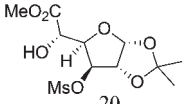| Entry	Substrate (% ee)	Product (% ee)	Yield (%)[a]
1	**1** (98.0)	**2** (98.0)	96
2	**3** (62.0)	**4** (62.0)[b]	97
3	**5** (>99.0)	**6** (>99.0)	97
4	**7** (97.0)	**8** (97.0)	94
5	**9** (40.0)	**10** (40.0)	95
6	**11** (40.0)	**12** (40.0)	88
7	**13** (69.0)	**14** (69.0)[b]	95
8	**15** (81.0)	**16** (81.0)[b]	92

[a] Isolated yield. [b] ee was determined by HPLC analysis of the corresponding O–Bz derivative.

Encouraged by this result, the generality of the methodology was further tested with several aromatic as well as aliphatic monosubstituted ethylene glycols having various functional groups and the results are summarized in Table 3. Under the reaction conditions, the aromatic monosubstituted ethylene glycols possessing functional groups such as –F, m-NO$_2$, and p-Me underwent smooth oxidation to give the corresponding α-hydroxy carboxylic acids in very good yields (Table 3, entries 1 and 3–6). Similarly, both cyclic and acyclic aliphatic monosubstituted ethylene glycols underwent clean

Table 4 Chemoselective oxidation of glycols derived from carbohydrate molecules

Entry	Substrate	Product	Yield[a] (%)
1	**17**	**18**	84
2	**19**	**20**	83
3	**21**	**22**	81
4	**23**	**24**	80
5	**25**	**26**	87

[a] Isolated yield.

oxidation to furnish the corresponding α-hydroxy acids in excellent yields (Table 3, entries 2, 7 and 8). The versatility of the methodology was further tested wi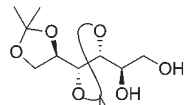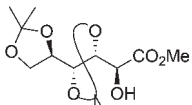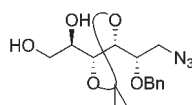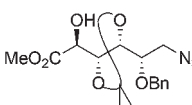th various glycols derived from carbohydrate molecules and the results are summarized in Table 4. Under the reaction conditions, the glycols, having both internal and terminal isopropylidene acetals, underwent smooth oxidation to give the corresponding α-hydroxy carboxylic acids in very good yields (Table 4, entries 1–5). Sensitive functional groups such as –OBn, –OMs, –N$_3$ and isopropylidene acetal were found to be stable under the reaction conditions.

Interestingly, the oxidation of phenylethylene glycol **1** using catalytic amounts of TEMPO is found to be equally effective under our reaction conditions and furnished the corresponding α-hydroxy acid **2a** in a slightly lower yield. The results are summarized in Table 5.[21]

Table 5 Oxidation of phenylethylene glycol **1** using a catalytic amount of TEMPO

Entry	TEMPO (eq.)	Time (h)	Yield of **2a** (%)
1	0.1	8	88
2	0.2	4.5	91
3	1.1	1.5	96

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Conclusions

In summary, a mild and highly efficient method has been developed for the direct synthesis of α-hydroxy acids from monosubstituted ethylene glycols. Intriguingly, our studies have shown that the solvent, pH and reaction temperature are very vital for the success of this TEMPO mediated oxidation of vicinal diol to α-hydroxy acid. Under the reaction conditions, optically active glycol furnishes the corresponding α-hydroxy acid in excellent yield with a high degree of optical purity. Several functional groups such as $-NO_2$, $-F$, $-OBn$, $-OMs$, $-N_3$ and isopropylidene acetal are found to be stable under the reaction conditions. Moreover, the catalytic version of this oxidation is found to be equally efficient. Since this reagent combination is more reliable and compatible with many functional groups, this method will find wide application in organic synthesis.[22]

Acknowledgements

Notes and references

1 G. M. Coppola and H. F. Schuster, *α-Hydroxy Acids in Enantioselective Syntheses*, VCH, Weinheim, 1997.

2 P. A. Grieco, T. Takigawa and T. R. Vedananda, *J. Org. Chem.*, 1985, **50**, 3111.

3 (*a*) G. Iwasaki, R. Kimura, N. Numao and K. Kondo, *Chem. Pharm. Bull.*, 1989, **37**, 280; (*b*) H. Urbach and R. Henning, *Tetrahedron Lett.*, 1984, **25**, 1143.

4 A. Furlenmeier, P. Quitt, K. Vogler and P. Lanz, *US Patent*, 3957758, 1976.

5 H. Bichel, K. Kocsis and H. Peter, *US Patent*, 4067979, 1978.

6 J.-P. Surivet and J.-M. Vatele, *Tetrahedron*, 1999, **55**, 13011.

7 J. Mills, K. K. Schmiegel and W. N. Shaw, *US Patent*, 4391826, 1983.

8 (*a*) S. Hanessian, *Total Synthesis of Natural Products: The Chiron Approach*, Pergamon Press, New York, 1983, ch. 2; (*b*) S. M. Roberts, in *Comprehensive Organic Chemistry*, ed. I. O. Sutherland, D. H. Barton and W. D. Ollis, Pergamon, Oxford, 1979, vol. 2, pp. 743–747; (*c*) J. O. Bunte, A. N. Cuzzupe, A. M. Daly and M. A. Rizzacasa, *Angew. Chem., Int. Ed.*, 2006, **45**, 6376.

9 (*a*) R. M. Hanson, *Chem. Rev.*, 1991, **91**, 437; (*b*) Y. Gao, J. M. Klunder, R. M. Hanson, H. Masamune, S. Y. Ko and K. B. Sharpless, *J. Am. Chem. Soc.*, 1987, **109**, 5765; (*c*) K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.*, 1973, **95**, 6136; (*d*) K. B. Sharpless and T. R. Verhoeven, *Aldrichimica Acta*, 1979, **12**, 63.

10 P. T. Ho and K. Y. Ngu, *J. Org. Chem.*, 1993, **58**, 2313.

11 M. P. Bousquet, R. M. Willemot, P. Monsan and E. Boures, *J. Mol. Catal. B: Enzym.*, 1998, **5**, 49.

12 For kinetic resolutions see: (*a*) F. F. Huerta, Y. R. S. Laxmi and J.-E. Backvall, *Org. Lett.*, 2000, **2**, 1037; (*b*) L. Tang and L. Deng, *J. Am. Chem. Soc.*, 2002, **124**, 2870. For enzymatic resolutions see: (*c*) H.-R. Huang, J.-H. Xu, Y. Xu, J. Pan and X. Liu, *Tetrahedron: Asymmetry*, 2005, **16**, 2113; (*d*) R. F. Campbell, K. Fitzpatrick, T. Inghardt, O. Karlsson, K. Nilsson, J. E. Reilly and L. Yet, *Tetrahedron Lett.*, 2003, **44**, 5477.

13 (*a*) M.-X. Wang, G. Lu, G.-J. Ji, Z.-T. Huang, O. Meth-Cohn and J. Colby, *Tetrahedron: Asymmetry*, 2000, **11**, 1123; (*b*) D. Zhu, H. Ankati, C. Mukherjee, Y. Yang, E. R. Biehl and L. Hua, *Org. Lett.*, 2007, **9**, 2561; (*c*) P. Kaul, A. Banerjee and U. C. Banerjee, *Biomacromolecules*, 2006, **7**, 1536; (*d*) G. DeSantis, Z. Zhu, W. A. Greenberg, K. Wong, J. Chaplin, S. R. Hanson, B. Farwell, L. W. Nicholson, C. L. Rand, D. P. Weiner, D. E. Robertson and M. J. Burk, *J. Am. Chem. Soc.*, 2002, **124**, 9024.

14 (*a*) W. Yang, J.-H. Xu, Y. Xie, Y. Xu, G. Zhao and G.-Q. Lin, *Tetrahedron: Asymmetry*, 2006, **17**, 1769; (*b*) D. Zhu, J. E. Stearns, M. Ramirez and L. Hua, *Tetrahedron*, 2006, **62**, 4535; (*c*) M.-T. Xiao, Y.-Y. Huang, X.-A. Shi and Y.-H. Guo, *Enzyme Microb. Technol.*, 2005, **37**, 589; (*d*) D. Zhu, Y. Yang, J. D. Buynak and L. Hua, *Org. Biomol. Chem.*, 2006, **4**, 2690; (*e*) S. M. Glueck, M. Pirker, B. M. Nestl, B. T. Ueberbacher, B. Larissegger-Schnell, K. Csar, B. Hauer, R. Stuermer, W. Kroutil and K. Faber, *J. Org. Chem.*, 2005, **70**, 4028; (*f*) J.-L. Vasse, V. Levacher, J. Bourguignon and G. Dupas, *Chem. Commun.*, 2002, 2256.

15 F. A. Davis and B.-C. Chen, *Chem. Rev.*, 1992, **92**, 919.

16 P. S. Kumar, A. Banerjee and S. Baskaran, *Angew. Chem., Int. Ed.*, 2010, **49**, 804.

17 (*a*) G. D. Vries and A. Schors, *Tetrahedron Lett.*, 1968, **54**, 5689; (*b*) P. Mastrorilli, G. P. Surama, C. F. Nobile, G. Farinola and L. Lopez, *J. Mol. Catal.*, 2000, **156**, 278; (*c*) T. Iwahama, Y. Yoshino, T. Keitoku, S. Sakaguchi and Y. Ishii, *J. Org. Chem.*, 2000, **65**, 6502; (*d*) A. Cisneros, S. Fernández and J. E. Hernández, *Synth. Commun.*, 1982, **12**, 833; (*e*) T. R. Felthouse, *J. Am. Chem. Soc.*, 1987, **109**, 7566; (*f*) K. Kandeda, K. Morimoto and T. Imanaka, *Chem. Lett.*, 1988, **17**, 1295; (*g*) C. Venturello and M. Ricci, *J. Org. Chem.*, 1986, **51**, 1599; (*h*) A.-K. C. Schmidt and C. B. W. Stark, *Org. Lett.*, 2011, **13**, 5788.

18 (*a*) M. Zhao, J. Li, E. Mano, Z. Song, D. M. Tschaen, E. J. J. Grabowski and P. J. Reider, *J. Org. Chem.*, 1999, **64**, 2564; (*b*) L. D. Luca, G. Giacomelli, S. Masala and A. Porcheddu, *J. Org. Chem.*, 2003, **68**, 4999; (*c*) C. S. Rye and S. G. Withers, *J. Am. Chem. Soc.*, 2002, **124**, 9756; (*d*) L. Ying and J. Gervay-Hague, *Carbohydr. Res.*, 2003, **338**, 835; (*e*) J. A. Cella, J. A. Kelley and E. F. Kenehan, *J. Org. Chem.*, 1975, **40**, 1860; (*f*) L. Huang, N. Teumelsan and X. Huang, *Chem. – Eur. J.*, 2006, **12**, 5246; (*g*) K. L. Reddy and K. B. Sharpless, *J. Am. Chem. Soc.*, 1998, **120**, 1207; (*h*) G. C. G. Pais and M. E. Maier, *J. Org. Chem.*, 1999, **64**, 4551; (*i*) P. L. Anelli, C. Biffi, F. Montanari and S. Quici, *J. Org. Chem.*, 1987, **52**, 2559; (*j*) D. L. Boger, R. B. Borzilleri

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and S. Nukui, *J. Org. Chem.*, 1996, **61**, 3561; (*k*) K. C. Nicolaou, C. N. C. Boddy, S. Natarajan, T.-Y. Yue, H. Li, S. Bräse and J. M. Ramanjulu, *J. Am. Chem. Soc.*, 1997, **119**, 3421; (*l*) D. L. Boger, S. H. Kim, Y. Mori, J.-H. Weng, O. Rogel, S. L. Castle and J. J. McAtee, *J. Am. Chem. Soc.*, 2001, **123**, 1862; (*m*) P. Gancitano, R. Ciriminna, M. L. Testa, A. Fidalgo, L. M. Ilharco and M. Pagliaro, *Org. Biomol. Chem.*, 2005, **3**, 2389.

19 (*a*) F. J. Aladro, F. M. Guerra, F. J. Moreno-Dorado, J. M. Bustamante, Z. D. Jorge and G. M. Massanet, *Tetrahedron Lett.*, 2000, **41**, 3209; (*b*) M. Shibuya, R. Doi, T. Shibuta, S. Uesugi and Y. Iwabuchi, *Org. Lett.*, 2012, **14**, 5006.

20 (*a*) S. Liang, Z. Xu and T. Ye, *Chem. Commun.*, 2010, **46**, 153; (*b*) A. Brar and Y. D. Vankar, *Tetrahedron Lett.*, 2006, **47**, 9035; (*c*) S. A. W. Gruner, V. Truffault, G. Voll, E. Locardi, M. Stöckle and H. Kessler, *Chem. – Eur. J.*, 2002, **8**, 4365; (*d*) M. Ikunaka, J. Matsumoto and Y. Nishimoto, *Tetrahedron: Asymmetry*, 2002, **13**, 1201.

21 The catalytic oxidation is a more cost effective method to run these reactions on a large scale. We thank one of the reviewers for suggesting this catalytic version.

22 *General experimental procedure*: To a stirred solution of compound **1** (138 mg, 1 mmol) and TEMPO (172 mg, 1.1 mmol) in acetone (6 mL) at 0 °C was added KBr (12 mg, 0.1 mmol) followed by 5% aqueous $NaHCO_3$ solution (2.6 mL). To this mixture at 0 °C, 4% NaOCl (3.7 mL, 2.0 mmol) was added dropwise and the resulting mixture was stirred at 0 °C. After completion of the reaction (~1.5 h), aqueous 5% $NaHCO_3$ solution (3.7 mL) was added, the solvent was removed under reduced pressure and the aqueous layer was washed with ether (2 × 10 mL) to remove TEMPO impurities. The aqueous layer was cooled to 0 °C, acidified to pH 6 with 1 N hydrochloric acid and then extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with water, brine and dried over anhydrous Na_2SO_4. The organic layer was then concentrated under reduced pressure and the crude compound was treated with diazomethane in ether to furnish the corresponding methyl ester **2**. The crude product **2** on column chromatographic purification over silica gel using 8–10% EtOAc in hexane as a solvent gradient afforded the pure methyl ester **2** (159 mg, 96%) as a white solid.

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