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# Concise Entry to Chiral 5-(4-Hydroxybutyl)-2(5*H*)-furanone via HTIB-Mediated Novel Oxidative Fragmentation: Formal Total Synthesis of (+)-Dubiusamine A

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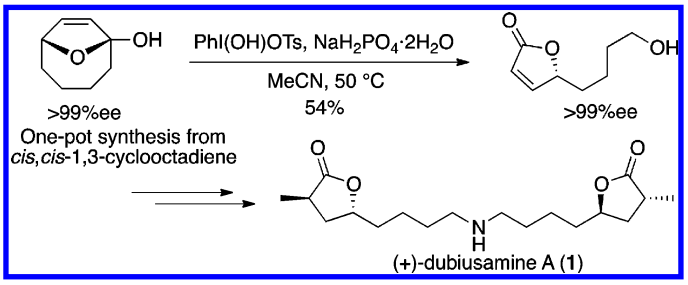
## ABSTRACT




**The concise synthesis of 5-(4-hydroxybutyl)-2(5*H*)furanone has been accomplished from 9-oxabicyclo[4.2.1]non-7-en-1-ol on the basis of HTIB [PhI(OH)OTs, a.k.a. Koser's reagent]-mediated novel oxidative fragmentation. Chiral (−)-(*R*)-5-(4-hydroxy-butyl)-2(5*H*)-furanone (>99% ee) was used for the formal total synthesis of (+)-dubiusamine A (1).**

The fertile nature of hypervalent iodine reagents has continuously spurred the sustainable development of synthetic organic chemistry.[1,2] We have recently reported a concise entry to both enantiomers of 8-oxabicyclo[3.2.1]-oct-3-en-2-one (**3**) via the HTIB [PhI(OH)OTs,[3] a.k.a. Koser's reagent]-mediated, novel intramolecular oxidative etherification of 4-hydroxy-cyclohept-2-enone (**2**),[4] which features the direct α′(C7)-functionalization[5] of **2** (Scheme 1).

During our effort toward expanding the synthetic scope of the HTIB-mediated oxidative etherification reaction, we encountered the unexpected fragmentation of 9-oxabicyclo-[4.2.1]non-7-en-1-ol (**4b**), which is a substantial tautomer of 4-hydroxycyclooct-2-enone (**4a**),[6] to give 5-(4-hydroxy-butyl)-2(5*H*)-furanone (**5**). Herein, we disclose a concise entry to highly enantiomerically enriched 5-(4-hydroxybutyl)-2(5*H*)-furanone (**5**) based on a sequential organocatalytic asymmetric Toste-Kornblum-DeLaMare rearrangement[6]

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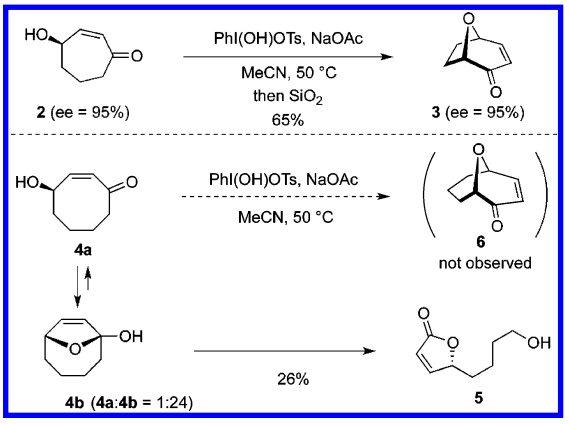
and HTIB-mediated oxidative fragmentation. We also demonstrate the synthetic use of **5** by transforming it into (+)-dubiusamine A (**1**), which was isolated from the crude base of *Pandanus dubius,*[7] a congener of a medicinally relevant tropical plant of the family Pandanaceae.[8]

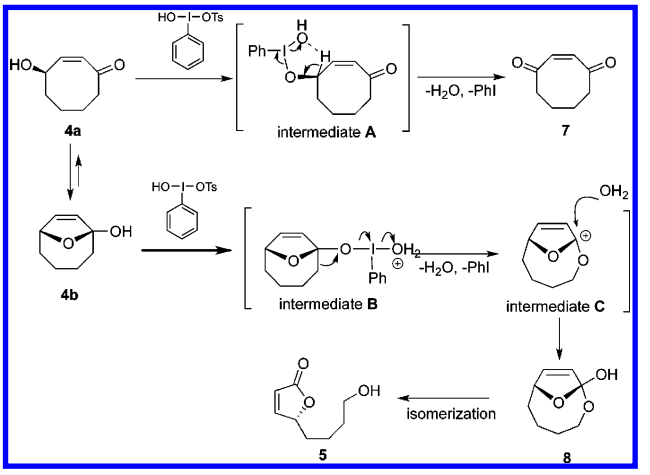
At the outset, we envisioned that 9-oxa-bicyclo[3.3.1]-non-3-en-2-one (**6**) could be obtained from 4-hydroxy-cyclooct-2-enone (**4a**)[9] by employing HTIB-mediated, intramolecular oxidative etherification (Scheme 1). The attempt was carried out using racemic **4**,[10] and unfortunately, the attempted intramolecular oxidative etherification using HTIB/NaOAc[4] gave not even a trace amount of **6**; instead, 5-(4-hydroxybutyl)-2(5*H*)-furanone (**5**) was obtained with modest yields (Scheme 1, Table 1, entries 1−3). The cause of the unexpected reaction is considered to be the reluctance of **4b** to tautomerize to **4a**, where HTIB reacts with **4b** at the hemiacetalic OH moiety to give the covalent intermediate **B**, from which oxidative fragmentation[11] occurred and the concomitant hydrolysis furnished the butenolide **5** (Scheme 2).[12]

**Scheme 1.** Oxidative Fragmentation




Prompted by the novel mode of the reaction as well as the potential use of the butenolide **5** as a building block for the synthesis of γ-lactone-containing natural products[13,14] (Figure 1), we then focused on identifying optimal conditions for oxidative fragmentation.

**Scheme 2.** Plausible Reaction Pathway for Oxidative Etherification



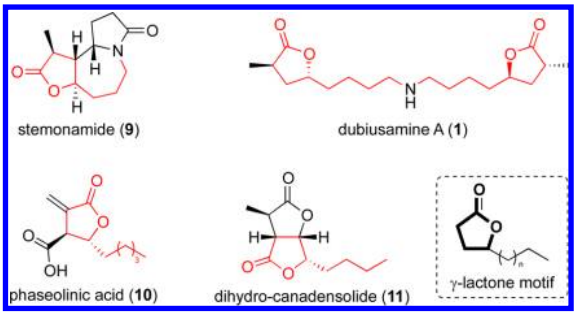




**Figure 1.** Natural products featuring γ-lactone moiety.

After the set of examinations summarized in Table 1, we found that the presence of $NaH_2PO_4 \cdot 2H_2O$ significantly improved the productivity of the reaction: treatment of **4a** with 1.5 equiv of HTIB in the presence of 1.4 equiv of $NaH_2PO_4 \cdot 2H_2O$ in MeCN at 50 °C afforded **5** with 54% yield (entry 10).

Having identified reliable conditions for conducting HTIB-mediated oxidative fragmentation to give **5**, we embarked on the formal total synthesis of (+)-dubiusamine A (**1**) to demonstrate the synthetic use of the reaction. The requisite starting material, namely, (1*S*,6*R*)-9-oxabicyclo[4.2.1]non-7-en-1-ol (−)-**4b**, was prepared via one-pot synthesis with 92% yield and > 99% ee[15] starting from

(9) $^1$H NMR indicated that 4-hydroxycyclooct-2-enone (**4a**) exists as a tautomeric mixture with 9-oxabicyclo[4.2.1]non-7-en-1-ol (**4b**) in a 1:24 ratio in $CDCl_3$ at rt.

(10) Racemic **4** was prepared in one-pot reaction from *cis,cis*-1,3-cyclooctadiene in 95% yield via photooxygenation ($O_2$ bubbling, 5 mol% tetraphenylprophyrin, 100 W tungsten lamp) and the following treatment with 2 equiv of $Et_3N$.

(11) Selected examples of oxidative ring fragmentation; (a) HgO/$I_2$: Suginome, H.; Yamada, S. *J. Org. Chem.* **1985**, *50*, 2489. *Tetrahedron* **1987**, *43*, 3371. $Pb(OAc)_4/I_2$: (b) Fuhrer, H.; Lorenc, L.; Pavlovic, V.; Rihs, G.; Rist, G.; Kalvoda, J.; Mihailovic, M. Lj. *Helv. Chim. Acta* **1981**, *64*, 703. IBDA/$I_2$: (c) Freire, R.; Marrero, J. J.; Rodríguez, M. S.; Suárez, E. *Tetrahedron Lett.* **1986**, *27*, 383. Iodosyl-benzene/$I_2$: (d) Arrmas, P.; Francisco, C. G.; Suárez, E. *Tetrahedron Lett.* **1993**, *34*, 7331. $FeSO_4$/$Cu(OAc)_2$: (e) Schreiber, S. L. *J. Am. Chem. Soc.* **1980**, *102*, 6163. $Pb(OAc)_4$ with γ-hydroxyalkylstannanes: (f) Nakatani, K.; Isoe, S. *Tetrahedron Lett.* **1984**, *25*, 5335. $Mn(OAc)_3/Cu(OAc)_2$: (g) Heiba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 524. $Pb(OAc)_4$/$Cu(OAc)_2$: (h) Rigby, J. H.; Psyn, A.; Warshakoon, N. *Tetrahedron Lett.* **2001**, *42*, 2047.

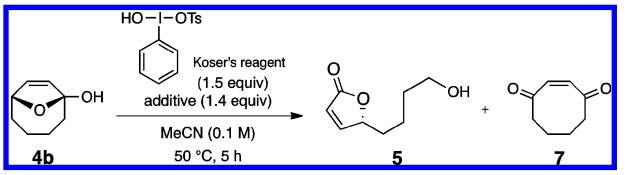
(12) According to a reviewer's comment, we examined the use of other iodine(III) reagents for this transformation. $PhI(OAc)_2$ resulted in no reaction after 24 h at 50 °C either in the presence or absense of $NaH_2PO_4$. $PhI(OCOCF_3)_2$ caused gradual decomposition of **4b** to give intractable polar byproducts under the same reaction conditions.

(13) (a) Bandichhor, R.; Nosse, B.; Reiser, O. *Top. Curr. Chem.* **2005**, *243*, 43. (b) Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9426.

(14) For recent synthesis of chiral butenolides, see: (a) Devalankar, D. A.; Chouthaiwale, P. V.; Sudalai, A. *Tetrahedron; Asymmetry* **2012**, *23*, 240. (b) Wu, Y.; Singh, R. P.; Li, D. *J. Am. Chem. Soc.* **2011**, *133*, 12458. (c) Mao, B.; Geurts, K.; Fananás-Mastral, M.; van Zijl, A. W.; Fletcher, S. P.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2011**, *13*, 948.

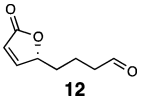
(15) The enantiomeric purity of the butenolide (−)-5 was determined after benzoylation. See Supporting Information.

**Table 1.** Optimization of Oxidative Fragmentation




| | | yield (%) | |
|---|---|---|---|
| entry | additive | **5** | **7** |
| 1[a,b] | AcONa | trace | 0 |
| 2 | | 29 | 0 |
| 3 | AcONa | 26 | 0 |
| 4[c] | AcOK | 28 | 4 |
| 5 | $LiOH \cdot H_2O$ | 34 | 0 |
| 6 | $KH_2PO_4$ | 29 | nd. |
| **7** | $KaHPO_4$ | 30 | nd. |
| 8 | $KHSO_4$ | 36 | nd. |
| 9 | $Na_2HPO_4$ | 45 | 0 |
| **10** | $\mathbf{NaH_2PO_4 \cdot 2H_2O}$ | **54** | **0** |

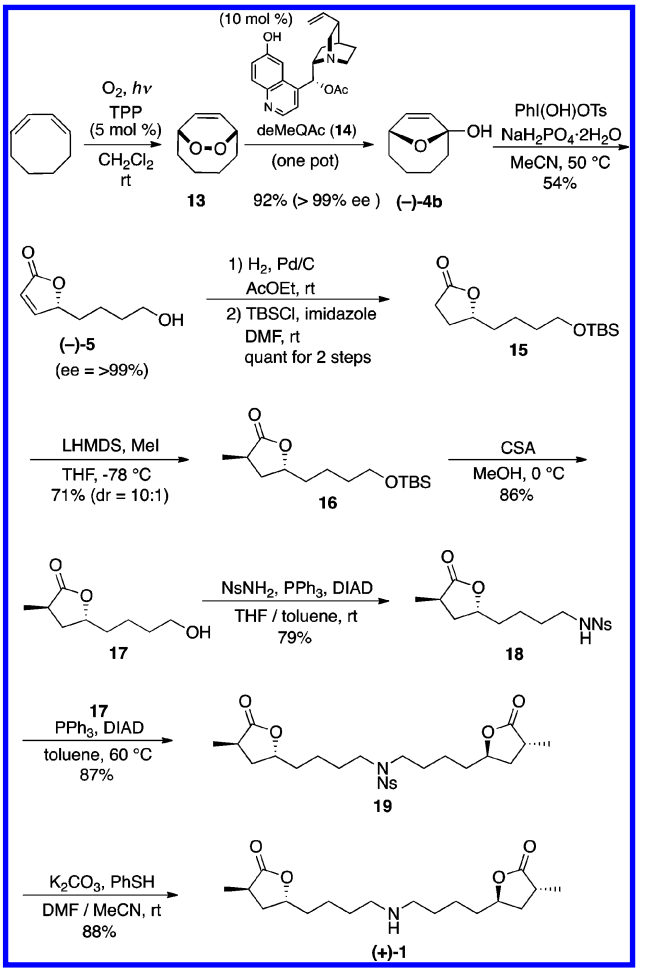
[a] Reaction was carried out at rt. [b] Reaction Time was 24 h. [c] **12** was obtained with 6% yield.




*cis,cis*-1,3-cyclooctadiene, through sequential photooxygenation to give the prochiral endoperoxide **13** and deMeQAc (**14**)-catalyzed Toste-Kornblum-DeLaMare rearrangement.[6] Upon treatment with 1.5 equiv of HTIB in the presence of 1.4 equiv of $NaH_2PO_4 \cdot 2H_2O$ in warm MeCN for 0.5 h, (−)-**4b** furnished (−)-**5** with 54% yield without the loss of enantiomeric integrity. Prior to the introduction of a C-2 methyl group, the butenolide moiety of (−)-**5** was hydrogenated and the primary hydroxyl group was masked as the TBS ether. The treatment of **15** with LHMDS and MeI allowed the diastereoselective α-methylation of the lactone ring to give **16** with a 10:1 (anti/syn) ratio. After the removal of the TBS group from **16** using camphorsulfonic acid in MeOH at 0 °C, the resultant alcohol **17** was subjected to the Mitsunobu reaction employing 2-nitrobenzenesulfonamide,[16] $PPh_3$, and DIAD in THF/toluene to give **18** in 79% yield, which was again subjected to the Mitsunobu reaction with alcohol **17** to give the nosyl[16]-protected symmetrical amide **19**. The treatment of **19** with $K_2CO_3$ and PhSH in MeCN-DMF affected the deprotection of the nosyl group. After carefully purifying the crude product using silica gel chromatography, diastereomerically pure (+)-**1** was obtained, Scheme 3. All the spectral data and the specific rotation of (+)-**1** were in good agreement with those reported by Takayama et al.,[7] which clearly determined the stereochemical course of the HTIB-mediated reaction of (−)-**4b**.

In summary, the concise enantioselective synthesis of 5-(4-hydroxybutyl)-2(5*H*)-furanone (**5**) has been accomplished

**Scheme 3.** Application to the Formal Synthesis of (+)-**1**




via the HTIB-mediated oxidative fragmentation of 9-oxabicyclo[4.2.1]non-7-en-1-ol (**4b**), which represents the further potential of hypervalent iodine reagents for organic synthesis. The synthetic use of (−)-**5** was demonstrated by a formal total synthesis of dubiusamine A (**1**). Since a chiral catalyst that leads to the asymmetric Toste-Kornblum-DeLaMare reaction of (+)-**4b** (>99% ee) has been established,[6] the present work will allow the realization of a concise entry to both enantiomers of **5**.

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**Supporting Information Available.** Experimental procedures and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.