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Concise Entry to Both Enantiomers of 8-Oxabicyclo[3.2.1]oct-3-en-2-one Based on Novel Oxidative Etherification: Formal Synthesis of (+)-Sundiversifolide

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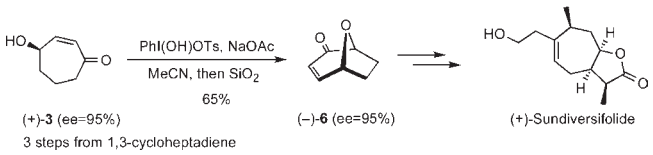
ABSTRACT



Both enantiomers of 8-oxabicyclo[3.2.1]oct-3-en-2-one (6) have been synthesized from 4-hydroxycyclohept-2-enone (3) on the basis of a novel oxidative cyclo-etherification using PhI(OH)OTs (Koser's reagent). (−)-(1*S*,5*R*)-8-Oxabicyclo[3.2.1]oct-3-en-2-one [(−)-6, 95% ee] was expeditiously transformed to (+)-sundiversifolide (1).

The diastereoselective functionalization of a cycloheptane derivative often poses challenges to synthetic chemists owing to the inherent conformational uncertainties. To address this issue, the structural motif of 8-oxabicyclo[3.2.1]octanes[1] with definite stereoelectronic basis has often served as a useful platform for the manipulation of cycloheptane derivatives.[2]

Current methods of securing an 8-oxabicyclo[3.2.1] octane skeleton rely predominantly on [4 + 3]-[3] or [5 + 2]-type[4] cycloaddition reactions: Unfortunately, they typically require many steps in the elaboration of the substrates, particularly in the case of enantioselective synthesis. We envisioned that 8-oxabicyclo[3.2.1]oct-3-en-2-one (**6**)[5] would be accessible from 4-hydroxycyclohept-2-enone (**3**) via an oxidative transformation.

In this paper, we disclose a concise entry to both enantiomers of 8-oxabicyclo[3.2.1]oct-3-en-2-one (**6**), featuring PhI(OH)OTs[6] (Koser's reagent)-mediated, intramolecular oxidative etherification[7] of 4-hydroxycyclohept-2-enone (**3**). We also demonstrate its use by converting (−)-**6** to (+)-sundiversifolide (**1**), which was isolated from the

(1) For reviews, see: (a) Hartung, I. V.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 1934. (b) Harmata, M. *Adv. Synth. Catal.* **2006**, *348*, 2297.

(2) For reviews, see: (a) Battiste, M. A.; Pelphrey, P. M.; Wright, D. L. *Chem.—Eur. J.* **2006**, *12*, 3438. (b) Harmata, M. *Chem. Commun.* **2010**, 8886.

(3) For selected examples, see: (a) Orugunty, R. S.; Wright, D. L.; Battiste, M. A.; Abboud, K. A. *Org. Lett.* **2002**, *4*, 1997. (b) Pelphrey, P. M.; Abboud, K. A.; Wright, D. L. *J. Org. Chem.* **2004**, *69*, 6931. (c) Chung, W. K.; Lam, S. K.; Lo, B.; Liu, L. L.; Wong, W.-T.; Chiu, P. *J. Am. Chem. Soc.* **2009**, *131*, 4556.

(4) For selected examples, see: (a) Hendrickson, J. B.; Farina, J. S. *J. Org. Chem.* **1980**, *45*, 3359. (b) Hendrickson, J. B.; Farina, J. S. *J. Org. Chem.* **1980**, *45*, 3361. (c) Sammes, P. G.; Street, L, J. *J. Chem. Soc., Chem Commun.* **1982**, 1056. (d) Wender, P. A.; Mascarenas, J. L. *Tetrahedron Lett.* **1992**, *33*, 2115. (e) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (f) Ali, M. A.; Bhogal, N.; Findlay, J. B. C.; Fishwick, C. W. G. *J. Med. Chem.* **2005**, *48*, 5655. (g) Snider, B. B.; Grabowski, J. F. *Tetrahedron Lett.* **2005**, *46*, 823. (h) Snider, B. B.; Grabowski, J. F. *Tetrahedron* **2006**, *62*, 5171. (i) Snider, B. B.; Wu, X. X.; Nakamura, S.; Hashimoto, S. *Org. Lett.* **2007**, *9*, 873. (j) Garnier, E. C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 7449. (k) Shimada, N.; Hanari, T.; Kurosaki, Y.; Takeda, K.; Anada, M.; Nambu, H.; Shiro, M.; Hashimoto, S. *J. Org. Chem.* **2010**, *75*, 6039.

(5) For a previous synthesis of **6**, see: Fattori, D.; Henry, S.; Vogel, P. *Tetrahedron* **1993**, *49*, 1649.

(6) (a) Moriarty, R. M.; Vaid, R. K.; Koser, G. F. *Synlett* **1990**, 365. (b) Koser, G. F. *Aldrichim. Acta* **2001**, *34*, 89. (c) Nabana, T.; Togo, H. *J. Org. Chem.* **2002**, *67*, 4362. (d) Ueno, M.; Nabana, T.; Togo, H. *J. Org. Chem.* **2003**, *68*, 6424. (e) Yamamoto, Y.; Togo, H. *Synlett* **2006**, 798. (f) Yamamoto, Y.; Kawano, Y.; Toy, P. H.; Togo, H. *Tetrahedron* **2007**, *63*, 4680. (g) Akiike, J.; Yamamoto, Y.; Togo, H. *Synlett* **2007**, 2168.

(7) For similar oxidative etherification induced by hypervalent indine compounds, see: (a) Fan, R.; Sun, Y.; Ye, Y. *Org. Lett.* **2009**, *11*, 5174. (b) Ye, Y.; Wang, L.; Fan, R. *J. Org. Chem.* **2010**, *75*, 1760. (c) Uyanik, M.; Okamoto, H.; Yasui, T.; Ishihara, K. *Science* **2010**, *328*, 1376.

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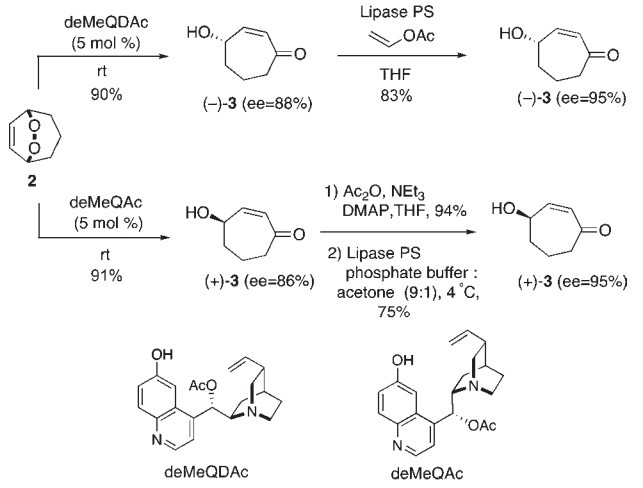
exudate of germinating sunflowers (*Helianthus annuus* L.) as a species-selective allelopathic substance.[8,9]

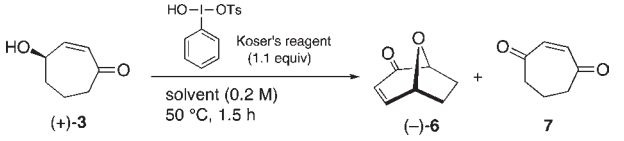
The preparation of the chiral starting material **3** (95% ee) was facilitated by cooperative asymmetric organo- and enzymatic catalysis (Scheme 1). Thus, the prochiral endoperoxide **2**, prepared in situ by the photooxygenation of 1,3-cycloheptadiene, was subjected to the chiral amine-catalyzed Kornblum–DeLaMare rearrangement[10] using 5 mol % of deMeQDAc (**4**) or deMeQAc (**5**), developed by Toste and co-workers,[10e] to give the (*S*)-(−)-4-hydroxy-cyclohept-2-enone (−)-**3** in 90% yield with 88% ee or (+)-**3** in 91% yield with 86% ee, respectively. On treatment of (−)-**3** (88% ee) with vinyl acetate in the presence of lipase PS in THF, (−)-**3** (95% ee) was obtained in 83% yield. Meanwhile, (+)-**3** (95% ee) was obtained from (+)-**3** (86% ee) in 71% yield, via acetylation and subsequent lipase-PS-catalyzed hydrolysis of acetate in phosphate buffer–acetone (9:1).[11]

Scheme 1. Preparation of Both Enantiomers of **3**



The projected oxidative etherification of **3** to give 8-oxabicyclo[3.2.1]oct-3-en-2-one (**6**) was an unprecedented reaction, but a clue was found by screening hypervalent iodine reagents.[7] Thus, upon treatment of **3** with PhI(OH)OTs[6] in warm MeCN, **6** was obtained in 36% yield accompanied by the enedione **7** in 8% yield (Table 1, entry 1). Attempts using other hypervalent iodine reagents, including 2-iodoxybenzoic acid (IBX), Dess–Martin periodinane (DMP), and $PhI(OAc)_2$,[7a] resulted in a simple oxidation of the allylic alcohol moiety to give **7** (data not shown). Changing the solvent to 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and DMF among others or increasing and/or decreasing the reaction temperature did not improve the yield (entries 3–8). The dilution of the reaction was found to be beneficial: the optimal reaction was performed at 0.1 M to obtain a yield of 44% (entry 9). We were delighted to find that the addition of NaOAc brought about marked improvement: the treatment of (+)-**3** (95% ee) with 1.5 equiv of PhI(OH)OTs in the presence of 1.4 equiv of NaOAc in MeCN at 50 °C, followed by addition of SiO_2 to the mixture, afforded (−)-**6** in 65% yield, the enantiomeric purity of which was preserved throughout the reaction.[11] Intriguingly, the addition of KOAc or CsOAc stopped the formation of (−)-**6**; instead, **7** was obtained chemoselectively (entries 11 and 12).

Table 1. Optimization of the Oxidative Cycloetherification



			yield[a]	
entry	solvent	additive	**6b**	**7**
1	MeCN		36	8
2	HFIP		9	3
3	DMF		29	1
4	DMSO		28	5
5	THF		11	1
6	benzene		26	4
7[b]	MeCN		28	0
8[c]	MeCN		28	6
9[d]	MeCN		44	4
10[d,e,f]	**MeCN**	**NaOAc (1.4 equiv)**	**65**	**3**
11[d,f]	MeCN	KOAc (1.4 equiv)	0	32
12[d,f,g]	MeCN	CsOAc(1.4 equiv)	0	61

[a] The ratio or products was determine by ^{1}H NMR spectrometry. [b] The reaction was carried out at 0 °C. [c] The reaction was carried out at 80 °C. [d] Concentration of the reaction was 0.1 M. [e] After the oxidative reaction, SiO_2 was added to crude mixture. [f] 1.5 equiv of Koser's reagent was used . [g] The reaction time was 24 h.

Plausible pathways of the PhI(OH)OTs-mediated oxidative etherification of (+)-**3** are outlined in Scheme 2. The enol form of **3** would react with a hypervalent iodine reagent to form intermediate **A** in preference to form **B**.[12] Then, an intramolecular S_N2 displacement by the hydroxy group should proceed to give (−)-**6** (path a), or an

(8) Isolation: Ohno, S.; Tomita-Yokotani, K.; Kosemura, S.; Node, M.; Suzuki, T.; Amano, M.; Yasui, K.; Goto, T.; Yamamura, S.; Hasegawa, K. *Phytochemistry* **2001**, *56*, 577.

(9) For total synthesis of sundiversifolide, see the following references. (+)-Form: (a) Yokoe, H.; Sasaki, H.; Yoshimura, T.; Shindo, M.; Yoshida, M.; Shishido, K. *Org. Lett.* **2007**, *9*, 969. (±)-Form:(b) Hashimoto, T.; Tashiro, T.; Sasaki, M.; Takikawa, H. *Biosci. Biotecnol. Biochem* **2007**, *71*, 2046. (+)- and (−)-forms: (c) Ohtsuki, K.; Matsuo, K.; Yoshikawa, T.; Moriya, C.; Tomita-Yokotani, K.; Shishido, K.; Shindo, M. *Org. Lett.* **2008**, *10*, 1247. (d) Shishido, K. *Heterocycles* **2009**, *78*, 873. (e) Matsuo, K.; Ohtsuki, K.; Yoshikawa, T.; Shishido, K.; Yokotani-Tomita, K.; Shindo, M. *Tetrahedron* **2010**, *66*, 8407.

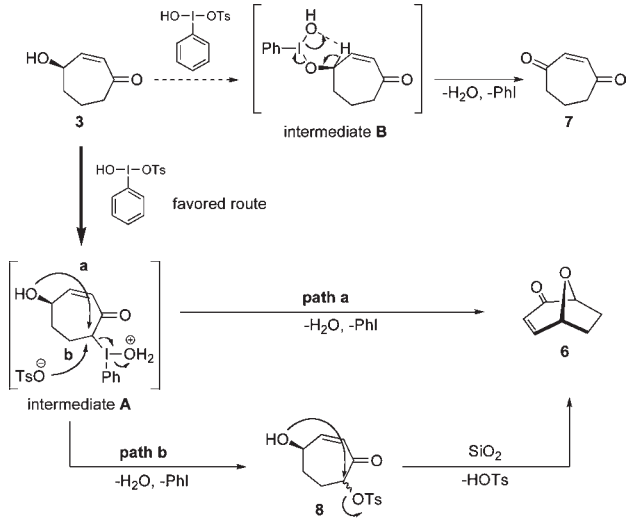
(10) (a) Kornblum, N.; DeLaMare, H. E. *J. Am. Chem. Soc.* **1951**, *73*, 880. (b) Hagenbuch, J. P.; Vogel, P. *J. Chem. Soc., Chem. Commun.* **1980**, 1062. For mechanistic studies, see: (c) Kelly, D. R.; Bansal, H.; Morgan, J. J. G. *Tetrahedron Lett.* **2002**, *43*, 9331. (d) Mete, E.; Altundas, R.; Secen, H.; Balci, M. *Turk. J. Chem.* **2003**, *27*, 145. (e) Staben, S. T.; Linghu, X.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12658.

(11) For the gram-scale preparation of both enantiomers of **6**, see the Supporting Information.

(12) For additional discussion, see the Supporting Information.

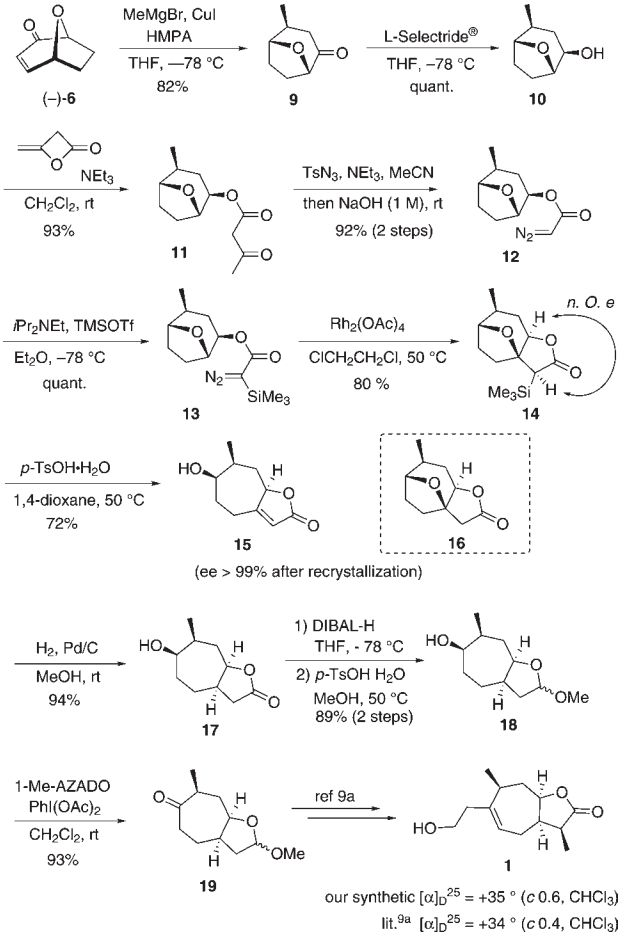
intermolecular S_N2 displacement by a tosylate might precede to give the α-tosyloxyenone **8**, which collapses to give (−)-**6** as above (path b). The reason why the oxidation of allylic alcohol by the addition of KOAc and CsOAc chemoselectively proceeded is under scrutiny.

Scheme 2. Plausible Reaction Pathway for the Oxidative Etherification



To demonstrate the use of **6**, we embarked on the formal total synthesis of the (+)-sundiversifolide (**1**).[8,9] As shown in Scheme 3, the synthesis commenced with the 1,4-addition of the cuprate reagent derived from methylmagnesium bromide and CuI onto (−)-**6** to furnish **9** as a single isomer[13] in good yield. The treatment of **9** with L-Selectride allowed the stereocontrolled reduction to give the desired β-alcohol **10** quantitatively.[14] The next focus of our endeavor was the installation of γ-lactone to form the 8-oxabicyclo[5.3.0]decane skeleton of the target molecule. To this end, the alcohol **10** was treated with diketene to give **11**, which was subjected to Regitz diazo-transfer reaction[15] to give the diazo ester **12**. We attempted the C−H insertion of **12** under various conditions, but the desired product was only obtained in a disappointing yield. After considerable experimentation, it was found that the adoption of the protocol of Bolm et al.,[16] introducing a TMS group at the α-position of the diazo group, was crucial for the desired C−H insertion to be successful. As such, upon treatment with a catalytic amount of $Rh_2(OAc)_4$ in boiling 1,2-dichloroethane, **13** furnished **14** as a single isomer in 80% yield, the stereochemistry of which was confirmed from NOESY correlations. With the bicyclic skeleton in hand, we attempted the selective cleavage of the oxo-bridge in **14**. Treatment with TBAF gave not only **15** but also **16**, which was considered to be furnished via the oxy-Michael addition of **15**. After various attempts, the best conditions identified were the use of *p*-TsOH in 1,4-dioxane at 50 °C. Sequential hydrogenation, DIBAL-H reduction, and acetalization with *p*-TsOH in MeOH provided the alcohol **18**, which was efficiently oxidized with the aid of a catalytic amount of 1-methyl-2-azaadamantane *N*-oxyl (1-Me-AZADO)[15] in the presence of $PhI(OAc)_2$ to give known ketone **19**[9a] in 93% yield. Compound **9** was conveniently converted to **1** in accordance with a previously reported procedure.[9a] It is interesting to note that previous enantioselective syntheses of **1** employed annulations of the advanced linear precursors for the construction of the cycloheptane motif of **1**,[9a,c] showing a clear contrast to our substrate-controlled approach.

Scheme 3. Application to the Formal Total Synthesis of **1**



In summary, we have developed a novel entry for both enantiomers of 8-oxabicyclo[3.2.1]oct-3-en-2-one (**6**) based on PhI(OH)OTs (Koser's reagent)-mediated, intramolecular oxidative etherification of 4-hydroxycyclohept-2-enone (**3**). The synthetic versatility of **6** as a chiral building block was demonstrated by its conversion to allelopathic bisnorsesquiterpene (+)-sundiversifolide (**1**). Further studies for expanding the synthetic scope of the novel oxidative etherification are underway.

(13) Reaction of 4-triethylsiloxy-cyclophet-2-enone with MeMgBr/CuI gave the 1,4-adduct as a single diastereomer, but the $NaBH_4$ reduction of which resulted in 1:1 diastereomeric alcohols, indicating an advantage of the oxa-bridged structure of **6**.

(14) $NaBH_4$-mediated reduction of **9** gave the α-alcohol selectively.

(15) Regitz, M. *Synthesis* **1972**, 351.

(16) Bolm, C.; Saladin, S.; Kasyan, A. *Org. Lett.* **2002**, *4*, 4631.

Acknowledgment. We thank Prof. Kozo Shishido of the University of Tokushima for providing us with the spectral data of the synthetic intermediate of sundiversifolide.

Supporting Information Available. Full experimental and characterization details for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.