ORGANIC LETTERS

2010
Vol. 12, No. 17
3882−3885

Asymmetric Synthesis of γ-Hydroxy α-Enones by 1,8-Diazabicyclo[5.4.0]undec-7-ene-Catalyzed Stereoselective Rearrangement of Chiral α-Sulfinyl Enones

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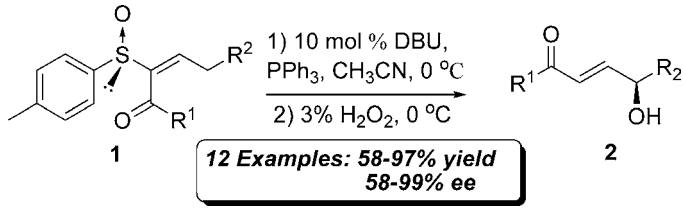
Received July 8, 2010

ABSTRACT



The asymmetric rearrangement of optically active α-sulfinyl enone 1 induced by catalytic DBU and triphenylphosphine gave optically active γ-hydroxy α-enone derivatives (up to 99% ee) in good yield following treatment with aqueous hydrogen peroxide.

The stereoselective synthesis of γ-hydroxy α-enones is an important topic in organic synthesis because these compounds are found in many natural products, most of which possess important bioactivity. For example, *Piper nigrum* components and their synthetic derivatives have been shown to have anticancer activity.[1] A fatty acid with strong cytotoxic activity has been isolated from corn extract.[2] Vancoresmycin has been isolated from *Amycolatopis* ST101170,[3] and recently, we have reported the isolation of alpinoids B and C from *Alpinia officinarum*. These compounds possess a chiral γ-hydroxy α-enone moiety and they are anticipated to possess anticancer and antiviral activity.[4] Nicolaou and co-workers reported a total synthesis of BE-43472B where have also a chiral γ-hydroxy α-enone was used in a key step.[5] Posner and Peterson reported an enantiocontrolled synthesis of γ-hydroxy-(*E*)-α,β-unsaturated sulfones and

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(1) (a) Wei, K.; Li, W.; Koike, K.; Pei, Y.-P.; Chen, Y.-J.; Nikaido, T. *J. Nat. Prod.* **2004**, *67*, 1005–1009. (b) Srinivas, Ch.; Sai Pavan Kumar, Ch. N. S.; China Raju, B.; Jayathirtha R, V.; Naidu, V. G. M.; Ramakrishna, S.; Diwan, P. V. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5915–5918.

(2) (a) Hayashi, Y.; Ishihara, N.; Takahashi, M.; Fujii, E.; Uenakai, K.; Masada, S.; Ichimoto, I. *Biosci. Biotech. Biochem.* **1996**, *60*, 1115–1117. (b) Kuga, H.; Ejima, A.; Mitsui, I.; Sato, K.; Ishihara, N.; Fukuda, K.; Uenakai, K. *Biosci. Biotech. Biochem.* **1993**, *57*, 1020–1021. (c) Matsushita, Y.; Sugamoto, K.; Nakama, T.; Matsui, T.; Hayashi, Y.; Uenakai, K. *Tetrahedron Lett.* **1997**, *38*, 6055–6058.

(3) Hopmann, C.; Kurz, M.; Bronstrup, M.; Wink, J.; LaBeller, D. *Tetrahedron Lett.* **2002**, *43*, 435–438.

(4) Sun, Y.; Matsubara, H.; Kitanaka, S.; Yasukawa, K. *Helv. Chim. Acta* **2008**, *91*, 118–123.

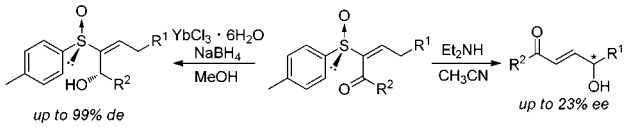
10.1021/ol1015724
Published on Web 08/12/2010

esters using enantioenriched α-selenyl aldehydes with EWG-stabilized carbanions.[6]

In the mid-1980s, we discovered a new 2,3-sigmatropic rearrangement involving cyclic enones and α-chloroalkyl sulfoxides under strongly basic conditions, which gave optically active cyclic γ-hydroxy α-enones (67−82% ee) in moderate yields.[7]

Nokami and co-workers reported that racemic β-keto-sulfoxides and aldehydes condensed in the presence of a secondary amine, in a Knoevenagel-type carbon chain elongation, and that this was accompanied by a Mislow−Evans-type rearrangement to give a racemic γ-hydroxy α-enone.[8] However, this report did not mention the chirality of the γ-hydroxyl group. Recently, we reported that the stereoselective Luche reduction of α-sulfinyl enones treated with ytterbium chloride hexahydrate and sodium borohydride in methanol proceeded in excellent yield and with high stereoselectivity (Scheme 1).[9] Subsequently, when an

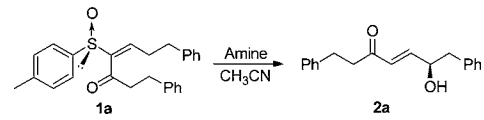
Scheme 1. Asymmetric Reduction and Sigmatropic Rearrangement of α-Sulfinyl Enones

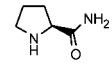
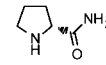


acetonitrile solution of chiral α-sulfinyl enone (1.0 equiv) in the presence of diethylamine was stirred for 2 h (procedure A, Supporting Information), γ-hydroxy α-enone was obtained in good yield, but the stereoselectivity was very low (Scheme 1 and Table S1, Supporting Information). As a consequence, we became interested in exploring the potential of this reaction to have its stereoselectivity improved using various amines and α-sulfinyl enones as chiral auxiliaries. Herein, we report on the use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-catalyzed sigmatropic rearrangement of α-sulfinyl enones with triphenylphosphine (PPh_3) leading to chiral γ-hydroxy α-enones in high ee.

Initial studies using (*Ss*,*E*)-1,7-diphenyl-4-(4-tolylsulfinyl)-hept-4-en-3-one **1a** as the substrate were aimed at determining the optimal stereoselective reaction conditions for the asymmetric rearrangement reaction using various amines. These results are summarized in Table 1. For the detailed

Table 1. Optimization of the Stereoselective Rearrangement of α-Sulfinyl Enone **1a** Using Various Amines



			2a	
entry[a]	amine (phosphine)	time (h)	yield (%)[b]	ee (%)[c]
1	Et_2NH	2	quant	4
2	Et_3N	2	89	6
3	*i*-Pr_2NH	2	46	10
4	Me_2NH	2	79	10
5	Morpholine	2	95	25
6	Piperidine	2	90	40
7		3	97	38
8		3	82	45
9	DABCO	0.5	63	80
10	DBU	0.5	19	**99**
11	PPh_3	12	68	22
12[d]	**DBU/PPh_3**	**0.5**	**45**	**99**

[a] Reaction conditions: **1a** (0.2 mmol), amine or PPh_3 (0.24 mmol), CH_3CN (2 mL), and the reactions were carried out at rt. [b] Isolated yield. [c] The ee was determined by HPLC equipped with a DAICEL IC-3 column. [d] DBU (10 mol %), PPh_3 (0.3 mmol), and CH_3CN (2 mL) was used at 0 °C.

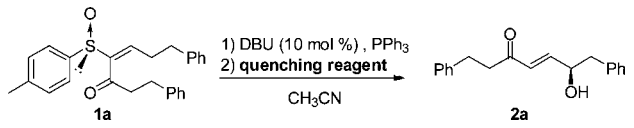
preparation of substrates **1a**−**l**, see the Supporting Information. Et_2NH and Et_3N provided **2a** in good yield but with almost no enantioselectivity when used for inducing the rearrangement of **1a** (Table 1, entries 1 and 2). The cyclic amines piperidine and morphorine gave excellent yields and somewhat better selectivity (Table 1, entries 5 and 6). The chiral amines L-prolinamide and D-prolinamide produced the same results as the cyclic amines (Table 1, entries 7 and 8). The bulky cyclic amine 1,4-diazabicyclo[2.2.2]octane (DABCO) displayed good stereoselectivity and moderate yield (Table 1, entry 9). We also found that DBU gave rise to excellent stereoselectivity; however, the yield was very low (Table 1, entry 10). On the other hand, when PPh_3 was used, **2a** was obtained in moderate yield and low stereoselectivity within 10 h (Table 1, entry 11).

Finally, use of a catalytic amount of DBU together with PPh_3 produced a somewhat better chemical yield of **2a** from **1a**, and the stereoselectivity was high (Table 1, entry 12). However, the product **2a** decomposed during the usual workup, thus decreasing the amount of the target compound.

Accordingly, we next attempted to find a more suitable system that incorporated appropriate quenching conditions for the DBU-catalyzed sigmatropic rearrangement. The asymmetric rearrangement yields following treatment with various quenching reagents are summarized in Table 2. We

(5) (a) Nicolaou, K. C.; Lim, Y. H.; Becker, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3444–3448. (b) Nicolaou, K. C.; Becker, J.; Lim, Y. H.; Lemire, A.; Neubauer, T.; Montero, A. *J. Am. Chem. Soc.* **2009**, *131*, 14812–14826.
(6) Peterson, K. S.; Posner, G. H. *Org. Lett.* **2008**, *10*, 4685–4687.
(7) (a) Satoh, T.; Motohashi, S.; Yamakawa, K. *Tetrahedron lett.* **1986**, *27*, 2889–2892. (b) Satoh, T.; Motohashi, S.; Tokutake, T.; Yamakawa, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2966–2973.
(8) (a) Nokami, J.; Nishimura, A.; Sunami, M.; Wakabayashi, S. *Tetrahedron Lett.* **1987**, *28*, 649–650. (b) Nokami, J.; Taniguchi, T.; Ogawa, Y. *Chem. Lett.* **1994**, 43–44. (c) Nokami, J.; Osafune, M.; Shiraishi, K.; Sumida, S.; Imai, N. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2947–2948. (d) Nokami, J.; Kataoka, K.; Shiraishi, K.; Osafune, M.; Hussain, I.; Sumida, S. *J. Org. Chem.* **2001**, *66*, 1228–1232. (e) Giardinà, A.; Marcantoni, E.; Mecozzi, T.; Petrini, M. *Eur. J. Org. Chem.* **2001**, *4*, 713–718.
(9) Miura, M.; Toriyama, M.; Motohashi, S. *Tetrahedron: Asymmetry* **2007**, *18*, 1269–1271.

Table 2. Optimization Studies of Efficiently Quenching Reagent in the Asymmetric Rearrangement of α-Sulfinyl Enone **1a**



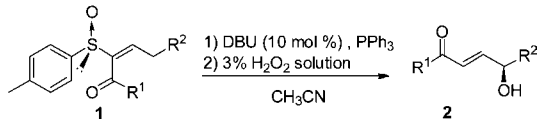
		2a	
entry[a]	quenching reagent	yield[b] (%)	ee[c] (%)
1	5% aq HCl solution	dec	
2	water	47	99
3	satd aq NH_4Cl solution	46	99
4	3% aq H_2O_2 solution	77	>99

[a] Reaction conditions: **1a** (0.2 mmol), DBU (0.02 mmol), PPh_3 (0.3 mmol), CH_3CN (4 mL); the reactions were carried out at 0 °C. [b] Isolated yield. [c] The ee was determined by HPLC equipped with a DAICEL IC-3 column.

first chose 5% aqueous HCl solution, but this did not have any quenching activity. Moreover, the product **2a** was completely decomposed (Table 2, entry 1). Water and saturated aqueous NH_4Cl solution gave the same low yields (Table 2, entries 2 and 3). Most notably, 3% aqueous H_2O_2 solution efficiently quenched this asymmetric reaction (Table 2, entry 4).

After optimization of the reaction conditions, the generality of the sigmatropic rearrangement was explored. A series of α-sulfinyl enones were examined (procedure B in the Supporting Information). The yields of the asymmetric sigmatropic rearrangement products ranged from good to excellent, and the results of our findings are summarized in Table 3. As shown

Table 3. Enantioselective Sigmatropic Rearrangement of Various α-Sulfinyl Enones



entry[a]	R^1	R^2	2	yield[b] (%)	ee[c] (%)
1	$PhCH_2CH_2$	$PhCH_2$	**2a**	77	>99
2	Ph	$PhCH_2$	**2b**	56	78
3	*i*-$PrCH_2$	$PhCH_2$	**2c**	76	97
4	$CH_3CH_2CH_2$	$PhCH_2$	**2d**	70	87
5	*i*-Pr	PhCH2	**2e**	68	90
6	Ph	nBu	**2f**	55	89
7	$PhCH_2CH_2$	nBu	**2g**	72	90
8	Ph_2CH	nBu	**2h**	97	58
9	Ph	*i*-Pr	**2i**	75	71
10	$PhCH_2CH_2$	*i*-Pr	**2j**	85	77
11	Ph	cyclopentyl	**2k**	92	74
12	$PhCH_2CH_2$	cyclopentyl	**2l**	84	86

[a] Reaction conditions: **1** (0.5 mmol), DBU (0.05 mmol), PPh_3 (1.5 mmol), CH_3CN (6 mL); the reactions were carried out at 0 °C for 30 min followed by quenching with 3% H_2O_2 at 0 °C. [b] Isolated yield. [c] The ee was determined by HPLC equipped with a DAICEL IC-3 column.

by entries 1−12, almost all of the reactions gave good enantioselectivity.

The absolute configuration at C(6) was assigned by application of the modified Mosher method.[10] Mosher acylation of **2g** and **2j** with both (α*S*)- and (α*R*)-α-methoxy-α-(trifluoromethyl)benzeneacetyl (MTPA) chloride yielded the C(6) (α*R*)- and (α*S*)-MTPA esters. The determination of $\Delta\delta$ value ($\delta_S - \delta_R$) for the protons neighboring C(6) led to the assignment of the (6*R*) configuration for **2g** and **2j** (Table 4).

Table 4. Characteristic ^1H NMR Data (600 MHz, $CDCl_3$) of the Mosher Esters Derived from **2g** and **2j**

	from **2g**			from **2j**		
	δ_S[a]	δ_R[b]	$\Delta\delta(\delta_S - \delta_R)$	δ_S[a]	δ_R[b]	$\Delta\delta(\delta_S - \delta_R)$
H−C (4)	6.04	6.21	−0.17	6.04	6.17	−0.13
H−C (5)	6.68	6.61	−0.07	6.60	6.67	−0.07
H−C (6)	5.40	5.41	(*R*)	5.59	5.59	(*R*)
H_3−C(10)	0.88	0.83	+0.05			
i-Pr (8)				0.91, 0.93	0.85, 0.87	+0.06, +0.06

[a] δ of (α*S*)-MTPA ester. [b] δof (α*R*)-MTPA ester.

However, the diphenyl-substituted compound (entry 8) gave excellent yield but only moderate enantioselectivity. R^1 = phenyl group compounds tended to give lower yields than the others (entries 2 and 6), and these compounds **2b** and **2f** were very unstable at room temperature. Thus, we believe that product **2b** and **2f** were decomposed in this system, and therefore the isolated yield was reduced.

On the basis of Nokami's report[8] and our own findings, a proposed mechanism for the DBU-catalyzed asymmetric sigmatropic rearrangement is illustrated in Figure 1. DBU deprotonates at the γ-position, and the enolate is generated in stage I. The protonated DBU may form a sterically hindered complex to intermediate **1**. Enolate attack on the lone-pair coordinated protonated DBU may then occur followed by asymmetric rearrangement (II).

This generates a chiral γ-oxysulfanyl α-enone (III) that undergoes oxidation and hydolysis. This generates the chiral γ-hydroxy α-enone and sulfinic acid in the final stage (IV).

In conclusion, we have developed an efficient method of carrying out a highly enantioselective sigmatropic rearrangement of α-sulfinyl enones utilizing catalytic quantities of DBU, with PPh_3, and aqueous H_2O_2 workup. This leads to good yields of chiral γ-hydroxy α-enone.

The reaction proceeds via a sigmatropic rearrangement.[11] The mild reaction conditions and short reaction times make this an attractive methodology for accessing

(10) (a) Kusumi, T.; Ooi, T.; Ohkubo, Y.; Yabuuchi, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 965–980. (b) Li, G.; Xu, M. L.; Chio, H. G.; Lee, S. H.; Jahng, Y. D.; Lee, C. S.; Moon, D. C.; Woo, M. H.; Son, J. K. *Chem. Phram, Bull.* **2003**, *51*, 262–264.

(11) (a) Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 2100–2104. (b) Evans, D. A.; Andrews, G. C.; Sims, C. L. *J. Am. Chem. Soc.* **1971**, *93*, 4956–4957.

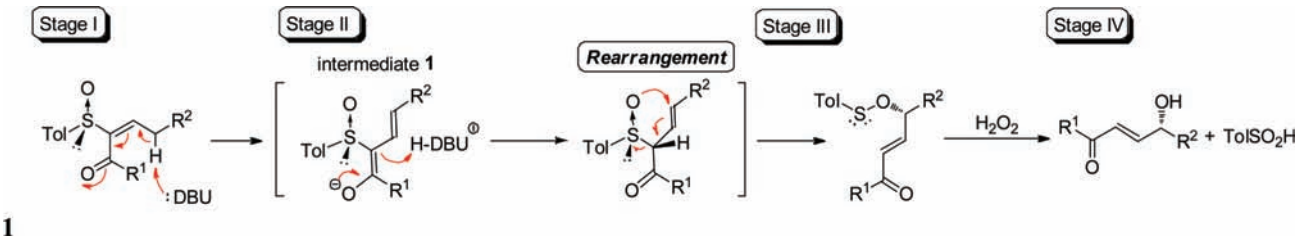


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Figure 1. Possible mechanism for the rearrangement of **1**.

chiral γ-hydroxy α-enones. Synthetic applications of the present reaction are currently being investigated in this laboratory.

Acknowledgment. This research was partially supported by the MEXT "Academic Frontier" project (2007) from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We thank Dr. Kouichi Metori (Analytical Center, School of Pharmacy, Nihon University) for performing the mass spectroscopy measurements. We also thank Mr. Atsuhito Suzuki (College of Science and Technology, Nihon University) for technical research.

Supporting Information Available: Detailed descriptions of the experimental procedure and full characterization of the new compounds shown in Table 3 This material is available free of charge via the Internet at http://pubs.acs.org.

OL1015724