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Diastereoconvergent Synthesis of *trans*-5-Hydroxy-6-Substituted-2-Piperidinones by Addition–Cyclization–Deprotection Process

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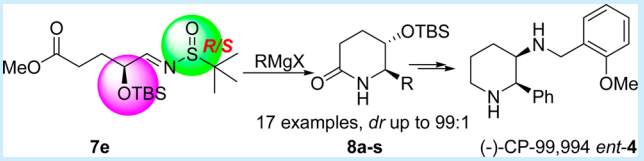
Supporting Information

ABSTRACT: A diastereoselective one-pot approach to access *trans*-5-hydroxy-6-substituted-2-piperidinones by an addition–cyclization–deprotection process has been developed, in which the stereogenic center at the C-6 position was solely controlled by α-OTBS group. The utility of this transformation is demonstrated by the asymmetric synthesis of the enantiomer of (−)-CP-99,994.



The discovery of a novel enantioselective reaction or versatile methodology for efficient carbon–carbon bond formation is one of the most challenging tasks in organic synthesis.[1] As a prime instance, the effective approach for the synthesis of chiral functionalized *trans*-5-hydroxy-6-substituted-2-piperidinones **1** (Figure 1) is very important in synthetic and

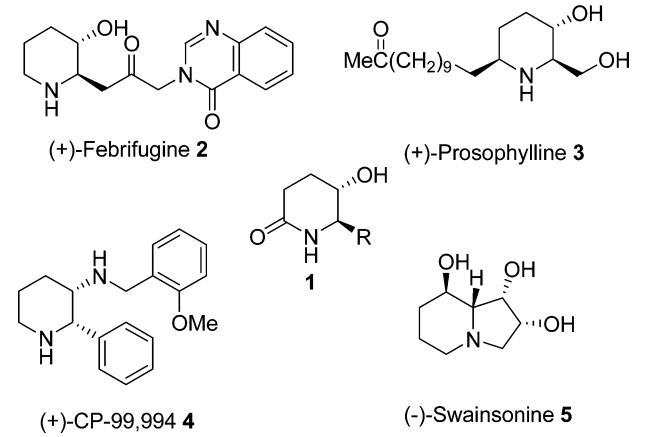


Figure 1. Structures of several natural products.

medicinal chemistry, because it serves as a substructure for numerous biologically relevant alkaloids and pharmaceutical agents.[2] Typical examples include antimalarial (+)-febrifugine **2**,[3] antibiotic and anesthetic *Prosopis* alkaloid (+)-prosophylline **3**,[4] as well as a clinical agent (+)-CP-99,994 **4**, which displays a variety of biological activities including neurogenic inflammation, pain transmission, and regulation of the immune response.[5] Moreover, the *trans*-2-alkyl-3-hydroxypiperidine unit is also embedded in the bicyclic structure of hydroxylated indolizidines, such as the α-mannosidase inhibitor (−)-swainsonine **5**.[6] As a result, the asymmetric synthesis of **1**, or its effective precursor, has attracted significant attention.[7,8]

In the past decade, chiral *N*-*tert*-butanesulfinamide and *N*-toluenesulfinamide, pioneered by Ellman and Davis respectively, are undoubtedly one of the most efficient classes of auxiliaries in modern organic synthesis,[9−11] especially for the asymmetric synthesis of chiral amines and their derivatives. The latter are extensively used as important intermediates for chiral ligands, agrochemicals, and pharmaceuticals.[12] In continuation of our efforts to explore utility of *N*-*tert*-butanesulfinyl imines, we have accomplished the synthesis of several bioactive natural products and their analogues.[13] Very recently, we reported a novel migration–addition of enantioenriched *N*-*tert*-butanesulfinyl iminoacetate through an intermolecular radical pathway.[14] As shown in Figure 2, Ellman has achieved a controllable Grignard addition to α-alkoxyaldimines, which could afford 1,2-*syn* or 1,2-*anti* amino alcohol from different diastereomers and under different reaction conditions (eqs 1 and 2 in Figure 2).[15]

In this work, we report a one-pot cascade process for highly diastereoselective synthesis of versatile *trans*-5-hydroxy-6-substituted-2-piperidinone skeleton **1** in good yields with high diastereoselectivities (eq 3), as well as the application in the asymmetric synthesis of (−)-CP-99,994 *ent*-**4**. The stereogenic center of C-6 was solely controlled by the α-alkoxy substitution.

As shown in Scheme 1, α-chiral *N*-sulfinyl aldimines **7a**–**f** were prepared to investigate our tandem reaction. The chiral ester **6** was prepared from L-glutamic acid using the known procedure.[16] Further conversion to the desired α-chiral *N*-sulfinyl aldimines **7a**–**e** were achieved through the following three steps: regioselective desilylation,[16b] oxidation with Dess–Martin periodinane[17] and subsequent condensation with racemic alkylsulfinamide in the presence of anhydrous cupric sulfate.[18] Meantime, α-chiral *N*-*tert*-butylsulfone aldimine **7f** was prepared from **7e** through oxidation by *m*-CPBA in 65% yield.

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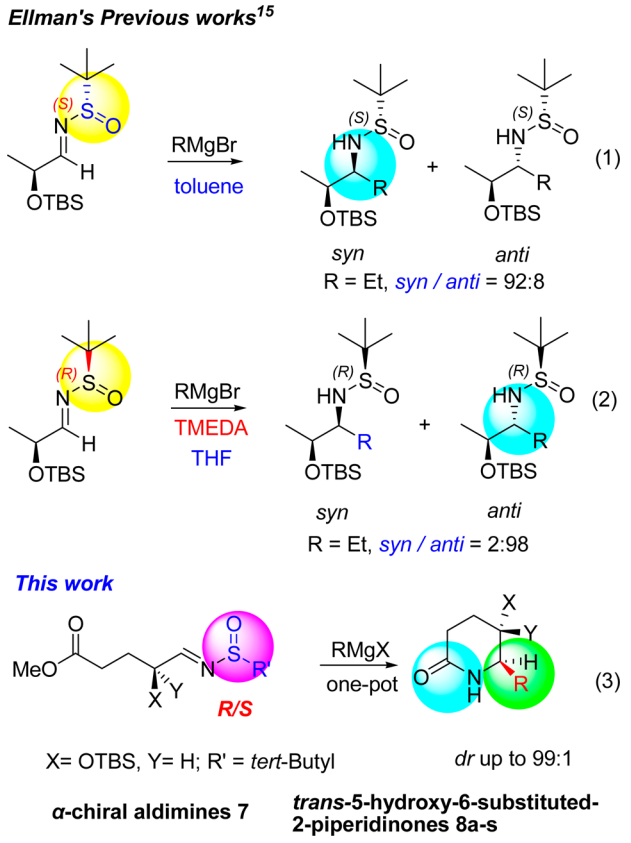
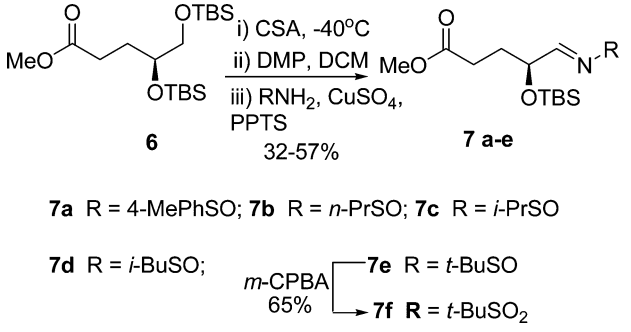


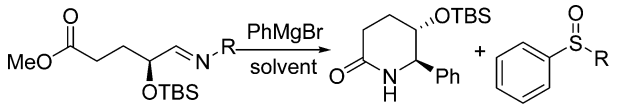
Figure 2. Our strategy to access chiral δ-lactams.

Scheme 1. Preparation of α-Chiral Aldimines 7a–f



Then, the intramolecular tandem reactions of α-chiral aldimines **7a–f** with Grignard reagents were investigated. When α-chiral aldimine 7**a** was treated with phenylmagnesium bromide at −78 °C, the desired product **8a** was obtained with high diastereoselectivity (dr > 99:1) in 39% yield (Table 1 entry 1). To improve the yield of this interesting chiral lactam **8a**, various aldimines with different alkyl groups at sulfur (**7b–f**) were screened, and the results are summarized in Table 1 (entries 2–6). Delightfully, α-chiral *N*-*tert*-butylsulfinyl aldimine **7e** significantly increased the yield of **8a**, up to 77% (Table 1 entry 6). When *N*-*tert*-butylsulfone aldimine **7f** was used, the reaction was very messy, and no desired product was formed (Table 1 entry 5). In addition, the reaction in tetrahydrofuran (THF) offered better conversion than in dichloromethane (DCM) (Table 1 entries 6 and 9). This tandem process likely went through a *N*-sulfinyl substituted lactam intermediate, which was formed through the attack of N anion toward the ester. The presence of *N*-carbonyl would

Table 1. Optimization of the Tandem Reactions



entry[a]	R	PhMgBr (equiv)	solvent	Y%[b]	*trans*:*cis*[c]
1	SOTol	3.0	THF	39	99:1
2	SOPr-*i*	3.0	THF	35	99:1
3	SOPr-*n*	3.0	THF	41	99:1
4	SOBu-*i*	3.0	THF	57	99:1
5	SO_2Bu-*t*	3.0	THF	0	–
6	SOBu-*t*	3.0	THF	77	99:1
7	SOBu-*t*	1.0	THF	21	99:1
8	SOBu-*t*	2.0	THF	49	99:1
9	SOBu-*t*	3.0	DCM	43	99:1

[a]The reactions were performed with α-chiral substituted aldimines **7a–f** (1.0 mmol), phenylmagnesium bromide (3 mL, 1.0 M in THF) in dry THF (5 mL) at −78 °C for 3 h. [b]Isolated yield. [c]dr was determined by HPLC or ^{1}H NMR.

weaken the S–N bond, leading to further nucleophilic displacement by excessive Grignard reagent. Actually, we isolated the byproducts, phenyl sulfoxides **9** in this process.[18b,19] Different amounts of Grignard reagent were also screened, and the results suggested that the Grignard addition to the aldimine and the cleavage of sulfinamide took place simultaneously (Table 1 entries 7–8). The effect of different chiral auxiliary in aldimine **7** was also studied. As shown in Table 3 (in the Supporting Information [SI]), both (S,S_S)-**7e** and (S,S_R)-**7e** generated the same product **8a**. Their corresponding enantiomers (R,S_S)-**7e** and (R,S_R)-**7e** were also subjected to the optimized conditions, both producing the desired enantiomer of **8a** (see the results of Table 3 and chiral HPLC in SI). This result suggested that the chiral sulfinamide moiety was not involved in the stereocontrol of this addition process.

Next, we turned our attention to investigate the scope and limitation of this intramolecular tandem addition–cyclization. A survey of different Grignard reagents was examined under the optimal conditions, as summarized in Table 2. When *para*- or *meta*-substituted phenyl Grignard reagents were used, the intramolecular tandem addition–cyclization proceeded smoothly with high diastereoselectivities in excellent yields (Table 2, entries 2–9). But *ortho*-substituted phenylmagnesium reagents led to significantly lower yields of desired products **8j–k** (Table 2, entries 10–11). Interestingly, 2-fluorophenylmagnesium bromide did not result in any desired addition–cyclization product (Table 2, entry 12). Bicyclic Grignard reagents, including α- and β-naphthyl magnesium bromides, also afforded the desired lactams, with the less hindered β-naphthyl magnesium bromide more efficient for this tandem process (Table 2, entries 13–14). Several sp^3 hybridized Grignard reagents were also screened, and the results showed that the steric dramatically affected the yields of products **8o–q** (Table 2, entries 15–17). It is worth mentioning that *tert*-butylmagnesium chloride did not attack the aldimine at all, and the starting material was fully recovered (Table 2, entry 18). Although BnMgBr could give corresponding product **8s** in 51% yield (Table 2, entry 19), the reaction with allylMgBr was very messy (Table 2, entry 20). Unfortunately, γ-lactam **10** was also tried by this process, but the yield was very low in the same

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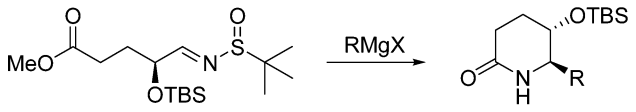
Table 2. Reactions with different Grignard reagents



7 e 8a-s

entry[a]	R	8a−t	Y%[b]	trans:cis[c]
1	Ph	**8a**	77	98:2
2	4-MePh	**8b**	93	99:1
3	4-MeOPh	**8c**	89	99:1
4	4-FPh	**8d**	93	99:1
5	4-PhPh	**8e**	82	99:1
6	3-MePh	**8f**	95	99:1
7	3-MeOPh	**8g**	90	99:1
8	3-CF_3Ph	**8h**	84	99:1
9	3-FPh	**8i**	89	99:1
10	2-MePh	**8j**	45	99:1
11	2-MeOPh	**8k**	40	99:1
12	2-FPh	**8l**	complex	--
13	*β*-naphthyl	**8m**	92	99:1
14	*α*-naphthyl	**8n**	53	99:1
15	cyclopropyl	**8o**	74	99:1
16	pentyl	**8p**	65	99:1
17	isopropyl	**8q**	48	99:1
18	*tert*-butyl	**8r**	NR	–
19	Bn	**8s**	51	99:1
20	Allyl	**8t**	complex	–

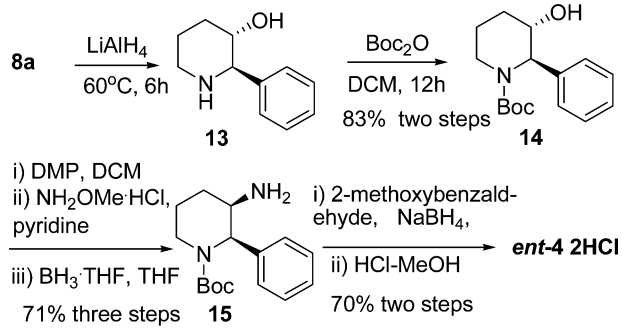
[a]The reactions were performed with *α*-chiral substituted aldimines **7e** (1.01 mmol), Grignard reagents (3 mL, 1.0 M in THF) in dry THF (5 mL) at −78 °C for 3 h. [b]Isolated yield. [c]dr was determined by HPLC or ^{1}H NMR.

condition[19] (see SI). To our disappointment, the efforts to prepare seven-membered lactam **11** turned out to be fruitless. Instead, the simple imine-addition product **12** was obtained with good diastereoselectivity (dr = 95:5) in 61% yield (see SI).[20]

The relative configurations of the products **8a−s** were unambiguously assigned as *trans*-form by X-ray crystallographical analysis of compound **8m** (see SI).

With chiral lactams **8a−s** in hand, we turned our attention to utilize this novel approach in the synthesis of natural products and pharmaceutical agents. (+)-CP-99,994 (**4**) is a nonpeptidic neurokinin NK1 receptor antagonist[5] with a variety of biological activities.[20] Treatment of chiral *δ*-lactam **8a** with lithium aluminum hydride ($LiAlH_4$) at 60 °C gave the piperidine **13**, which was treated with Boc_2O in DCM in the presence of catalytic amount DMAP to give compound **14** in 83% overall yield. Oxidation of **14** with Dess−Martin periodinane (DMP),[17] followed by oxime formation with *O*-methyl hydroxyamine hydrochloride ($NH_2OMe{\cdot}HCl$) and subsequent reduction with borane, produced the desired *cis*-2,3-disubstituted amine **15** with high diastereoselectivity (dr = 95:5) in 71% overall yield. The introduction of an *o*-methoxybenzyl group was accomplished by the reaction with 2-methoxybenzaldehyde in the presence of sodium borohydride ($NaBH_4$). Finally, the *N*-Boc protective group was removed by a saturated solution of hydrogen chloride in methanol to give (−)-CP-99,994·2HCl *ent*-**4** {$[\alpha]^{25}_D$ = −87.1 (*c* 0.36, CH_3OH); lit.[21i] +87.5 $[\alpha]^{23}_D$ (*c* 0.74, CH_3OH) for **4**} in quantitative yield (Scheme 2). The spectroscopic and physical data of the synthetic (−)-CP-99,994 dihydrochloride *ent*-**4** were identical to the reported data.[5,21]

Scheme 2. Application in Asymmetric Synthesis of (−)-CP-99,994·2HCl *ent*-4



In summary, we established a novel and one-pot approach for highly diastereoselective synthesis of versatile chiral building blocks **1** by treatment of *α*-alkoxyaldimines containing the *ω*-ester group with Grignard reagents. The reaction went through an intramolecular tandem sequence of addition−cyclization−deprotection, and the stereogenic center of C-6 was solely controlled by *α*-alkoxy substitution. This novel approach provides an efficient synthesis of libraries of chiral *trans*-5-hydroxy-6-substituted-2-piperidinones with synthetic value. In addition, the utility of chiral *δ*-lactams **8a** in the enantioselective synthesis of specific targets has been demonstrated by a concise synthetic route to (−)-CP-99,994 *ent*-**4**.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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(19) For the preparation of compound **10** and its material see Supporting Information.

(20) For the preparation of compound **12** and its material see Supporting Information.

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