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N-Sulfinyl β-Amino Weinreb Amides: Synthesis of Enantiopure β-Amino Carbonyl Compounds. Asymmetric Synthesis of (+)-Sedridine and (–)-Allosedridine

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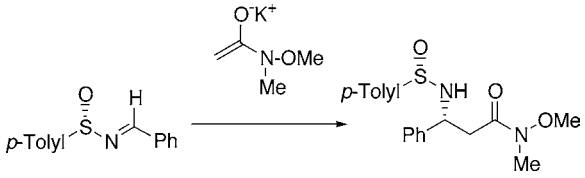
ABSTRACT



***N*-Sulfinyl β-amino Weinreb amides are prepared by condensation of sulfinimines with the potassium enolate of *N*-methoxy-*N*-methylacetamide. These new chiral building blocks are useful for the asymmetric synthesis of β-amino carbonyl compounds, as illustrated here by the concise enantioselective syntheses of sedum alkaloids (+)-sedridine and (–)-allosedridine.**

Unlike nonracemic N-protected α-amino aldehydes and ketones, which are valuable and widely used building blocks for the asymmetric synthesis of amine derivatives,[1] β-amino carbonyl compounds have found relatively few applications. However, β-amino carbonyl moieties are not only found in natural products,[2] but are potentially useful intermediates for Wittig-type condensations[3−7] and natural product,[4,5] 1,3-amino alcohol,[8] and β-amino acid synthesis. What has undoubtedly impeded their general use in asymmetric syntheses is the lack of convenient methods for their preparation as single enantiomers. For example, β-amino aldehydes are usually not isolated but prepared in solution because of their tendency to self-condense.[9] However, in 1998, we disclosed that certain sulfinimine-derived *N*-Cbz and *N*-Boc β-amino aldehydes are stable crystalline solids and could be used in the stereoselective synthesis of alkaloids such as (+)-phenylpiperidine and (+)-dihydropinidine.[3] In this paper, we report a general solution to the problem of β-amino carbonyl asymmetric construction employing new sulfinimine-derived enantiopure *N*-sulfinyl β-amino Weinreb amides.

Weinreb amides are valuable carbonyl equivalents for the synthesis of carbonyl compounds.[10] Although β-amino Weinreb amides have been described previously, they have

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(9) Asymmetric synthesis of β-amino carbonyl compounds: reduction of β-amino esters or nitriles, see refs 3 and 8 of this article. Toujas, J.-L.; Jost, E., Vaultier, M. *Bull. Soc. Chem. Fr*, **1997**, *134*, 713. Arndt-Eistert reaction, see ref 6 of this article.

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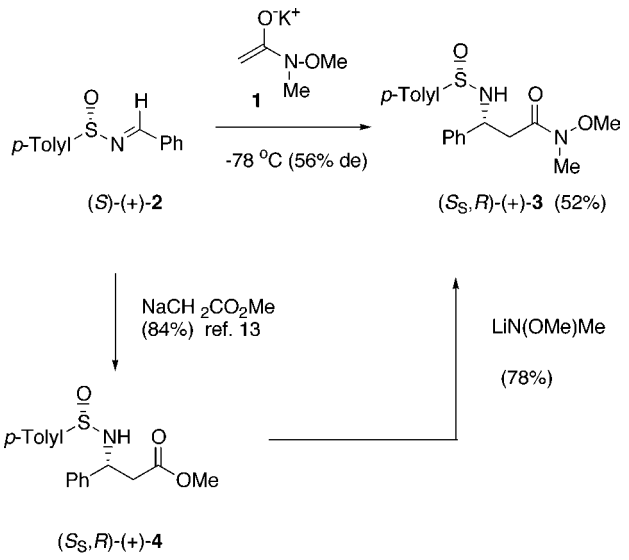
found relatively few uses because of difficult syntheses and/or problems in removal of the N-substituents.[11] Importantly, we have found that addition of the potassium enolate of commercially available *N*-methoxy-*N*-methylacetamide **1** to (*S*)-(+)-*N*-benzylidene-*p*-toluenesulfinamide (**2**) affords the corresponding *β*-amino Weinreb amide **3** in 56% de and 52% isolated yield of the major diastereoisomer (Scheme 1). Use

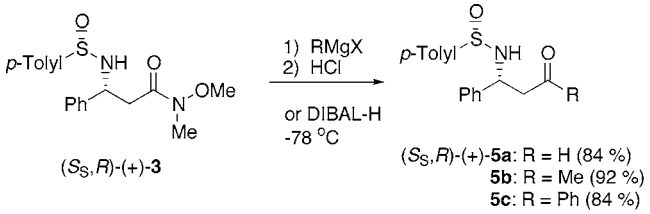
Scheme 1



of the 2-methoxynaphthyl or *tert*-butane sulfinyl auxiliaries resulted in poorer des and yields. However, it is worth noting that the diastereoselectivities for the addition of **1** to other aliphatic, alkenyl, and aromatic sulfinimines (see below) were consistently >95% de.[12] Alternatively, addition of 5 equiv of lithium *N*,*O*-dimethylhydroxyamine to (S_S,*R*)-(+)-methyl *N*-(*p*-toluenesulfinyl)-3-amino-3-phenyl propanoate (**4**),[13] prepared by addition of the sodium enolate of methyl acetate to (*S*)-(+)-**2**, gave (S_S,*R*)-(+)-**3** in 78% yield. This serves to establish the absolute stereochemistry of the product resulting from the addition of **1** to (*S*)-(+) **2** as *R*. Usually, the addition of organometallic reagents to sulfinimines can be predicted assuming six-member chairlike transition states where the metal ion is coordinated to the sulfinyl oxygen, and the results described here are in accordance with these observations.[14]

N-Sulfinyl *β*-amino Weinreb amide (S_S,*R*)-(+)-**3**, despite the presence of the acidic sulfinamide proton, reacts with various organometallic regents normally, affording the corresponding *β*-amino carbonyl compounds in good yield (Scheme 2). Thus, treatment of (+)-**3** with 5 equiv of

Scheme 2

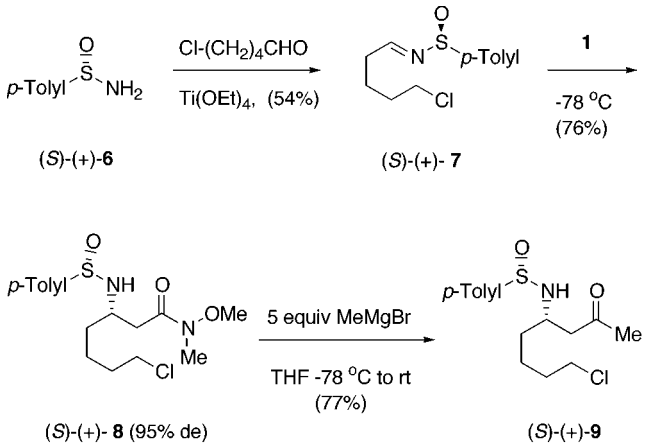


DIBAL-H in THF at −78 °C affords (*R*)-(+)-**5a** in 84% yield.[3] With 5 equiv of methylmagnesium bromide or phenylmagnesium bromide in THF, warming from −78 °C to room temperature furnishes the methyl and phenyl ketones (*R*)-(+)-**5b** and (*R*)-(+)-**5c** in 92 and 84% yields, respectively.

The sedum alkaloids are a large family of 2-substituted and 2,6-disubstituted piperidines having various combinations of carbonyl and hydroxyl functionalities in the side chains, many of which feature the 1,3-amino alcohol moiety.[15] These types of alkaloids have memory-enhancing properties and may be effective in treating Alzheimer's disease.[16] That *N*-sulfinyl *β*-amino Weinreb amides may provide general entry into this important class of piperidine alkaloids is illustrated by the asymmetric synthesis of (+)-sedridine (**14**) and (−)-allosedridine (**15**).[17]

Our synthesis begins with the preparation of the requisite sulfinimine, (*S*)-(+)-*N*-(6-chloropentylidine)-*p*-toluene-sulfinamide (**7**), in 54% yield by condensation of 5-chlorovaleroaldeyde with commercially available (*S*)-(+)-*p*-toluenesulfinamide (**6**) using $Ti(OEt)_4$ (Scheme 3).[18] Treatment

Scheme 3



of (+)-**7** with potassium enolate **1** gives the corresponding *β*-amino Weinreb amide (*S*)-(+)-**8** in 76% yield and >95% de. Reaction of the amide with 5 equiv of MeMgBr in ether gave the methyl ketone (*S*)-(+)-**9** in 77% yield.

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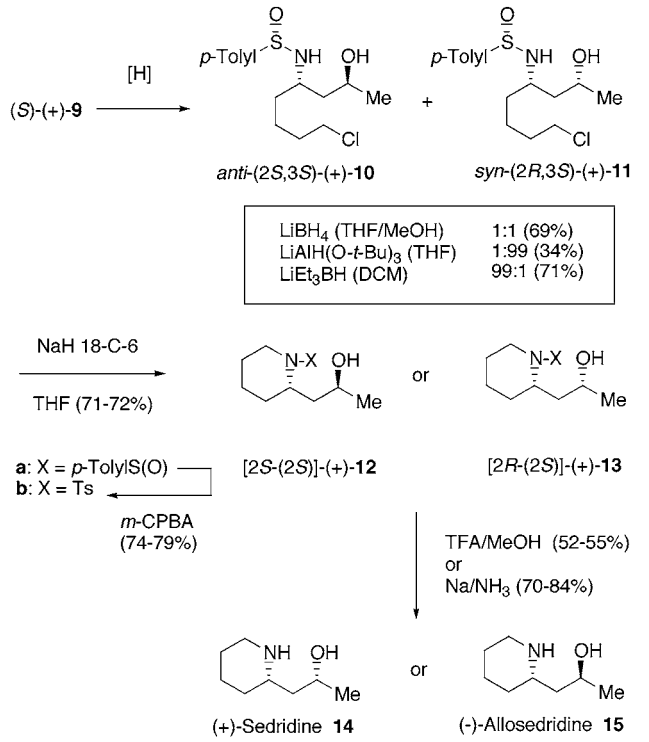
(12) Results of these studies will be reported separately in due course.

(13) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M. *J. Org. Chem*. **1995**, *60*, 7037.

(14) For reviews on the chemistry of sulfinimines, see: (a) Zhou, P.; Chen, B.-C.; Davis, F. A. In *Advances in Sulfur Chemistry*; Rayner, C. M., Ed.; JAI Press: Stamford, CT, 2000; Vol. 2, pp 249−282. (b) Davis, F. A.; Zhou, P.; Chen. B.-C. *Chem. Soc. Rev*. **1998**, *27*, 13. (c) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res*. **2002**, *35*, 984.

Stereoselective reduction of amino ketone **9** was next explored. With $LiBH_4$ in THF, a 1:1 separable mixture of the anti:syn 1,3-amino alcohols **10** and **11**, in a combined yield of 69%, resulted (Scheme 4). Reduction with Super-

Scheme 4



Hydride ($LiEt_3BH$) in DCM gave only the anti product (2*R*,3*S*)-(+)-**10** in 71% yield. While lithium tri-*tert*-butoxyaluminohydride in THF afforded exclusively the syn amino alcohol (2*R*,3*S*)-(+)-**11**, the yield was only 34%. Attempts to improve the yield by increasing the reaction time, temperature, or amount of reducing reagent resulted in poor yields, attributable to reactions at the chloro group. The structural assignments of the alcohols ultimately rests with their conversions into **14** and **15** (see below); however, the ^{13}C NMR of the C(2) carbons in the anti and syn alcohols appeared at δ 63.86 and 67.63 ppm, respectively. The relatively few examples of the stereoselective reduction of β-amino ketones[19,20] suggests that the modest-to-good 1,3-asymmetric induction can be interpreted using arguments similar to those invoked for the hydroxy-directed reduction of β-hydroxy ketones.[21] Here a reagent such as lithium tris-(*tert*-butoxy)aluminohydride will deliver an external hydride via a six-membered chelate involving the keto and amino groups, while anti selectivity results from intramolecular hydride delivery from a group bonded to the sulfinyl nitrogen.

With the acyclic 1,3-amino alcohols in hand, cyclization to hydroxy piperidines [2*S*-(2*S*)]-(+)-**12a** and [2*R*-(2*S*)]-(+)-**13a** was readily accomplished by stirring with NaH/THF in the presence of 30 mol % 18-crown-6 for 1 h. Isolation by chromatography afforded these materials in 71−72% yield. Although removal of the *N*-sulfinyl protecting group was accomplished in 52−55% yield by brief stirring with TFA/MeOH, the alkaloids were contaminated with up to 10% of the *p*-tolylsulfinyl byproducts. An improved method for isolation of **14**/**15** involved oxidation of the *N*-sulfinyl groups in **12a**/**13a** to the tosylates, **12b**/**13b**, with *m*-CPBA. Reductive cleavage of the sulfonamides, as reported by Gallagher et al.,[17c] with Na/liquid NH_3, afforded the pure alkaloids in 70−84% yield. The structures of (+)-sedridine (**14**) and (−)-allosedridine (**15**) were confirmed by comparison of their properties with literature values, as well as conversion to their *N*-Cbz derivatives.[17]

In summary, the asymmetric synthesis of *N*-sulfinyl β-amino Weinreb amides by addition of the potassium enolate of *N*-methoxy-*N*-methylacetamide to sulfinimines or by the reaction of *N*-sulfinyl β-amino esters with lithium *N*,*O*-dimethylhydroxyamine is described. These new chiral building blocks are expected to provide general access to enantiopure β-amino carbonyl compounds that are valuable intermediates for asymmetric synthesis. The utility of these new β-amino carbonyl compounds is illustrated in the concise asymmetric syntheses of the sedum alkaloids (+)-sedridine (**14**) and (−)-allosedridine (**15**).

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

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