

Asymmetric Synthesis of Substituted Tropinones Using the Intramolecular Mannich Cyclization Reaction and Acyclic *N*-Sulfinyl β -Amino Ketone Ketals

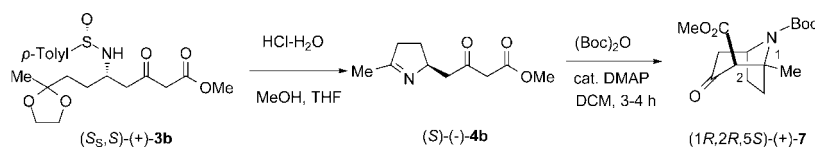
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ABSTRACT



Sulfinimine-derived, enantiopure *N*-sulfinyl β -amino ketone ketals on hydrolysis give dehydropyrrolidine ketones that on treatment with $(\text{Boc})_2\text{O}$ /DMAP afford substituted tropinones in good yield.

The continuing interest in the synthesis and biosynthesis of the tropane alkaloids, the 8-azabicyclo[3.2.1]octane ring system, is because of the significant biological properties of several members of this class of heterocycles including (–)-cocaine (**1**) and atropine (**2**) (Figure 1).¹ The impetus for most of the synthetic studies has been the search for useful

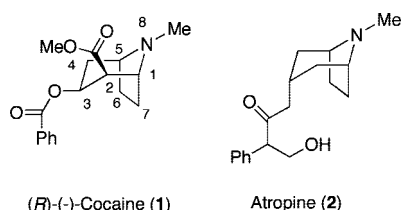


Figure 1. Important tropanes.

cocaine-type analogues (antagonists and agonists). Many syntheses of cocaine analogues employ advanced starting materials such as tropinone and cocaine itself.² Other

procedures to access the tropane skeleton include cycloaddition and intramolecular nucleophilic substitution reactions, Michael addition reactions, iminium ion cyclizations, and ring-closing metathesis procedures.³ Relatively few of these methods are asymmetric.³

Rapoport prepared (–)-**1** from glutamic acid using an intramolecular nucleophilic substitution reaction to form the tropane ring.⁴ Cha prepared (+)-cocaine (**1**) by desymmetrization of tropinone using a chiral lithium base and an aldol reaction to install the axial carbomethoxy group.⁵ Most asymmetric syntheses of this ring system employ some type of a cycloaddition reaction.^{3,6–10} For example, Mans and Pearson synthesized (+)-cocaine (**1**) in 86% ee using a 2-azaallyl-lithium [3 + 2] cycloaddition reaction to prepare a *meso*-

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(3) For an excellent summary of these reactions, see: (a) Mans, D. M.; Pearson, W. H. *Org. Lett.* **2004**, *6*, 3305. (b) Mans, D. M. Aza-Bridged Bicyclic Amines From (2-Azaallyl)stannanes and the Total Synthesis of (+)-Cocaine. *Ph.D. Thesis*, Univ. Michigan, Ann Arbor, MI, USA, 2004.

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pyrrolidine dialdehyde which was then subjected to an asymmetric proline-catalyzed intramolecular enol-*exo*-aldol reaction.^{3a} Recently, Reddy and Davies described the enantioselective synthesis of substituted tropanes using a rhodium-catalyzed [4 + 3] cycloaddition reaction of vinyl diazoacetates with *N*-Boc pyrroles.^{10a} With few exceptions,¹⁰ most syntheses are multistep, low overall yielding procedures which do not provide easy access to ring-substituted examples, particularly at the bridgehead positions of the tropane skeleton. We describe here the application of acyclic *N*-sulfinyl β -amino ketone ketals and the intramolecular Mannich cyclization reaction for the asymmetric synthesis of substituted tropanones.

The acid-catalyzed intramolecular Mannich cyclization reaction between an *N*-sulfinyl β -amino ketone and an aldehyde is an important method for the asymmetric synthesis of stereodefined substituted piperidines (Figure 2).^{11–13} We employed this protocol in highly efficient asymmetric

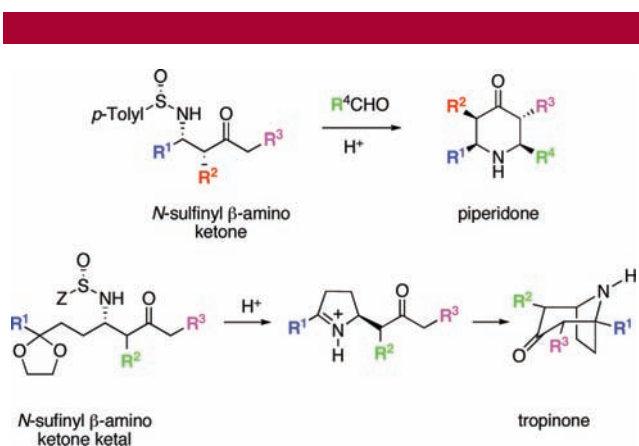


Figure 2. Intramolecular Mannich cyclizations.

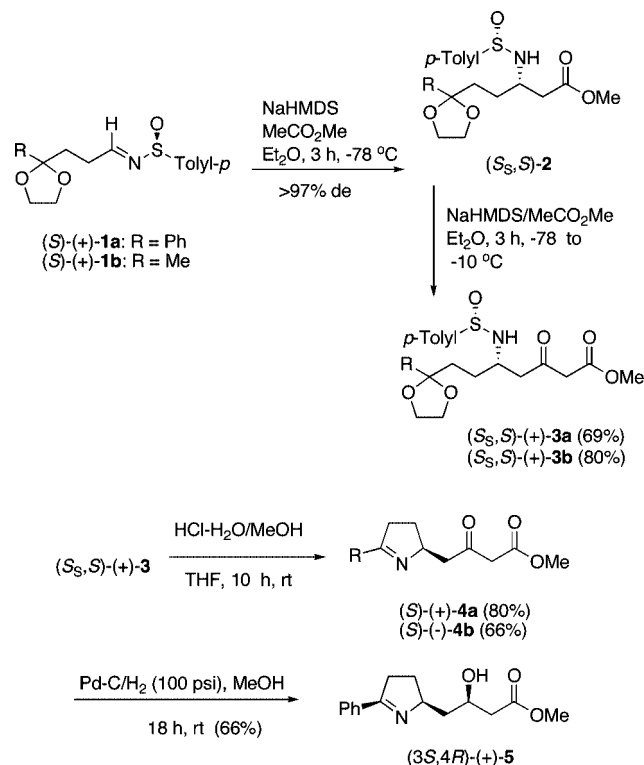
syntheses of the trisubstituted piperidine, (–)-nupharamine,¹⁴ and indolizidine alkaloids (–)-209B¹⁵ and (–)-223A.¹⁶ Enantiopure *N*-sulfinyl β -amino ketones are prepared by reaction of Grignard reagents with *N*-sulfinyl β -amino Weinreb amides.^{17,18} We reasoned that substituted tropinones would result if the Mannich cyclization were to occur at a pyrrolidine ring iminium ion that is also attached to the ketone unit. Hydrolysis of an acyclic *N*-sulfinyl β -amino ketone ketal could generate such a dehydropyrrolidine species, which under acidic conditions would form an iminium ion that could cyclize to the tropinone (Figure 2).¹⁹

Treatment of masked oxo sulfinimines (*S*)-(+)-**1a** ($R = \text{Ph}$) and (*S*)-(+)-**1b** ($R = \text{Me}$) with an excess of the sodium enolate of methyl acetate gave mixtures of the β -amino ester **2** and the desired *N*-sulfinyl δ -amino β -ketoester ketals (*S*_S,*S*)-(+)-**3**.²⁰ In these cases, the solution was recooled to -78°C , and an additional 5 equiv of the enolate was added, affording (*S*_S,*S*)-(+)-**3a** and (*S*_S,*S*)-(+)-**3b** in 69% and 80%

isolated yields, respectively. This contrasts with earlier studies where δ -amino β -ketoesters were prepared in excellent yield and high de by reaction of sulfinimines with an excess of the sodium enolate.²¹

When the *N*-sulfinyl δ -amino β -ketoester ketals (*S*_S,*S*)-(+)-**3** were treated with 3 N HCl/MeOH in THF at rt for 3 h, the tropinone was not formed, but rather the dehydropyrrolidines (*S*)-(+)-**4a** and (*S*)-(-)-**4b** in 80 and 66% yields, respectively (Scheme 1). Evidence for the formation of **4**, rather than the isomeric tropinone, is the presence of the imino carbons at δ 171–179 ppm in ¹³C NMR in addition to the keto and ester carbons at δ 200–210 and δ 165 ppm, respectively. In the ¹H NMR spectra, the Me protons in (–)-**4b** appear downfield at δ 2 ppm compared to δ 1.0–1.3 ppm for these protons in the corresponding tropinones (see below). Surprisingly, when (*S*)-(+)-**4a** was hydrogenated (Pd–C) at 100 psi for 8 h, hydroxy dehydropyrrolidine (+)-**5** was formed as a single isomer in 60–70% yield (Scheme 1).²²

Scheme 1. Synthesis of *N*-Sulfinyl δ -Amino β -Ketoester Ketals and Their Hydrolysis



Evidence for the reduction of a keto group rather than the imine is the presence of the imino carbon at δ 171 ppm and the absence of the keto carbon at δ 201 ppm.

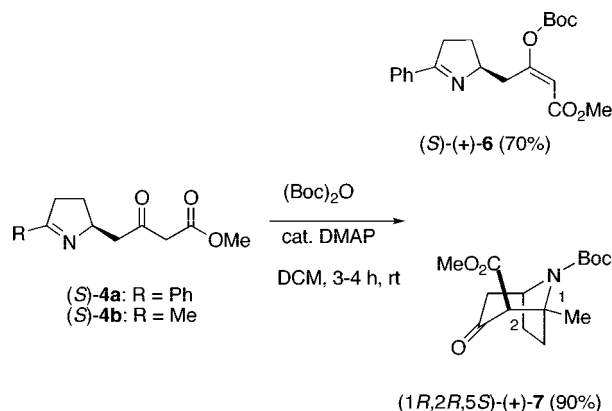
Reaction of imine (*S*)-(+)-**4a** with (Boc)₂O and a catalytic amount of DMAP resulted in formation of enol carbonate (*S*)-(+)-**6** in 70% yield. The vinylic proton at δ 5.9 ppm in the ¹H NMR and the dehydropyrrolidine carbon at δ 175 ppm in the ¹³C NMR support this structural assignment. NOE studies are consistent with the *E*-geometry for (+)-**6**. Importantly, when (*S*)-(-)-**4b** was

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treated with (Boc)₂O/cat.-DMAP, the Mannich cyclization resulted in tropinone (+)-**7** in excellent yield (Scheme 2). However, (+)-**7** was formed as a 70:30 inseparable

Scheme 2. Mannich Cyclization of Dehydropyrrolidines



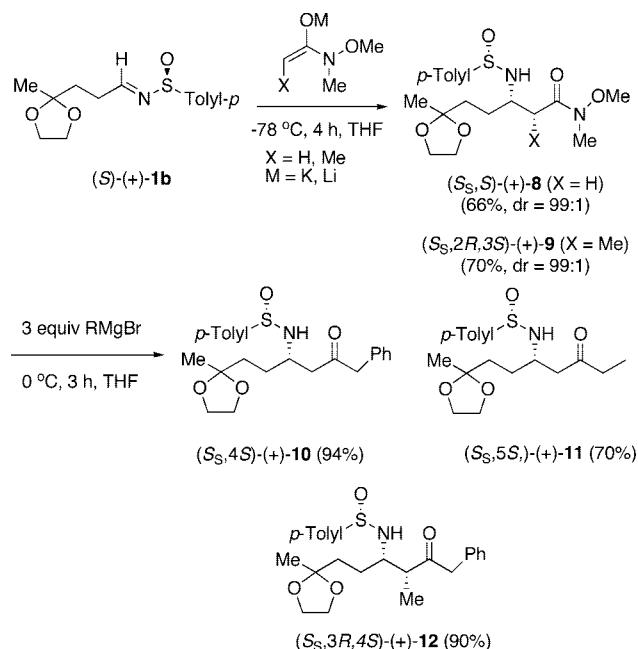
mixture of tropinones that are epimeric at C-2. The major epimer is assigned as having the C-2 carbomethoxy group in the axial position in analogy to the related tropinone reported by Thomas et al. in their racemic approaches to the alkaloid stemofoline.¹⁹ It is likely that the imino phenyl group in (*S*)-(+)-**4a** sterically inhibits the Mannich cyclization.

To further define the scope of the Mannich cyclization of dehydropyrrolidine ketone, the keto moiety was next varied. Masked oxo Weinreb amides (*S*_S,*S*)-(+)-**8** and (*S*_S,2*R*,3*S*)-(+)-**9** were prepared in good yield and high dr by reaction of (*S*)-(+)-**1b** with the potassium enolate of *N*-methoxy-*N*-methylacetamide^{17a} and the lithium enolate of *N*-methoxy-*N*-methylpropylamide,^{17b} respectively (Scheme 3).

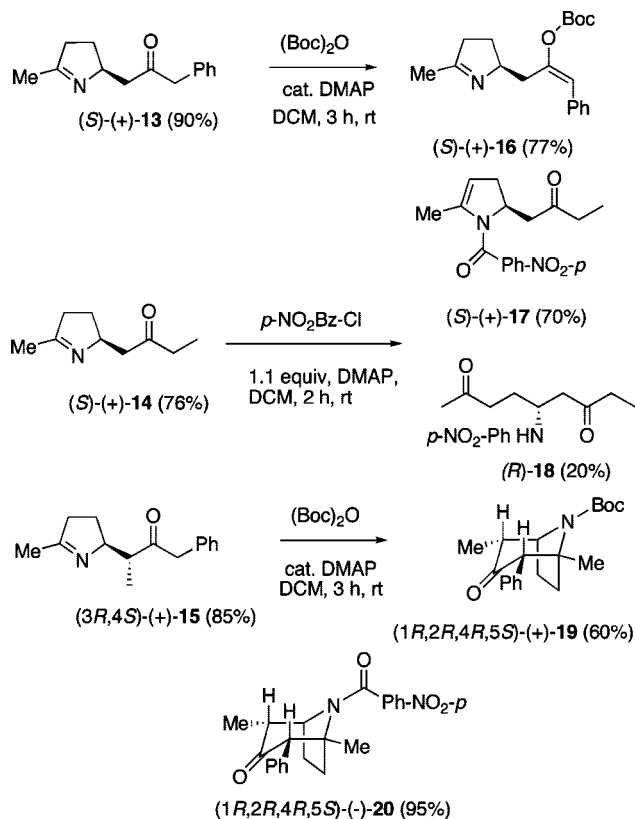
Treatment of the Weinreb amides (*S*_S,*S*)-(+)-**8** and (*S*_S,2*R*,3*S*)-(+)-**9** with benzylmagnesium chloride gave ketones (*S*_S,*S*)-(+)-**10** and (*S*_S,3*R*,3*S*)-(+)-**12** in excellent yield, while ethylmagnesium chloride with (*S*_S,2*S*,3*S*)-(+)-**8** gave ketone (*S*_S,3*S*)-(+)-**11** in good yield (Scheme 3).

As expected, reacting ketones **10–12** with 3 N HCl–MeOH in THF gave the corresponding dehydropyrrolidine ketones **13–15** in good yield (Scheme 4). When (*S*)-(+)-**13** was treated with (Boc)₂O/cat.-DMAP, the enol carbonate (*S*)-(+)-**16** resulted in 77% yield (Scheme 4). There was no reaction of (*S*)-(+)-**14** with (Boc)₂O/cat.-DMAP. However, reaction with *p*-nitrobenzoyl chloride (*p*-NO₂–Bz–Cl) and 1.1 equiv of DMAP, to generate a more electrophilic acyliminium ion species, failed to give the tropinone, but gave the isomeric enamide (*S*)-(+)-**17** in 70% yield. Evidence for the enamide structure comes from HMQC experiments which show the enamide proton at 4.97 ppm and the carbon attached to it at 112.8 ppm. The quaternary C–N carbon is coupled to the vinyl hydrogen. The pyrrolidine Me and C-2 protons are broadened due to the amide rotamers. Under acidic conditions, the enamide hydrolysis product,

Scheme 3. Synthesis of β-Amino Ketone Ketals



Scheme 4. Mannich Cyclization of Dehydropyrrolidine Ketones



(*R*)-(-)-**18**, was also formed. This product is apparently formed in the workup because it was not detected in the crude reaction mixture.

Remarkably, (3*R*,4*S*)-(+)-**15** gave tropinone (+)-**19** as a single isomer in 60% yield with (Boc)₂O/cat.-DMAP, and with *p*-nitrobenzoyl chloride/DMAP a 95% yield of tropinone (–)-**20** was formed. NOE studies suggest a syn relationship between C-2 and C-4 protons where the Ph and Me substituents occupy the equatorial positions in (+)-**19** and (–)-**20**. These results were confirmed by an X-ray crystal structure of (–)-**20** (see Supporting Information).

In (S)-(+)-**13**, the bulky phenyl group may inhibit the Mannich cyclization favoring enol carbonate formation. In (S)-(+)-**14**, enamide formation is apparently much faster than enolization due to the greater acidity of the intermediate pyrrolidine C-2 acyliminium ion proton (Scheme 4). However, the fact that (3*R*,4*S*)-(+)-**15** gave tropinone (+)-**19** in good yield suggests that other factors may be of importance

in determining whether the intermediate acyliminium ion forms the enol carbonate, deprotonates, or undergoes the Mannich cyclization. One thought is that the α-Me group in (+)-**15** somehow inhibits enol carbonate formation favoring the Mannich cyclization.

In summary, sulfinimine-derived *N*-sulfinyl β-amino ketone ketals and the intramolecular Mannich cyclization reaction represent a valuable new method for the asymmetric synthesis of substituted tropinones including those having substituents at the bridgehead positions.

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Supporting Information Available: Full experimental and spectroscopic data for all new compounds are provided. X-ray data, ORTEP, and CIF for compound (S)-(–)-**20** are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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