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# Intramolecular Tandem Isomerization–Mannich Reaction as a New Route Towards Aminocyclopentitols

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**Keywords:** Aminocyclopentitols / Iron / Mannich reaction / Domino reactions / Alcohols

A new efficient synthetic strategy has been developed to prepare aminocyclopentitols. It is based on an iron-catalyzed tandem isomerization–Mannich reaction and uses chiral *N*-*tert*-butanesulfinamide as a chiral auxiliary. This methodology has been applied to the enantiocontrolled synthesis of a mannostatin A analogue, as well as isomers of known fucosidase and glycosidase inhibitors.

## Introduction

Aminocyclitols are important compounds from a biological point of view, as many of them have demonstrated potent inhibition properties against various types of glycosidases.[1] On the basis of this activity, they are of much potential interest for the treatment of diabetes, cancer, and bacterial and viral infections for instance. This aminocyclopentitol structure is found in various natural products such as mannostatins or trehazoline, as well as in synthetic analogues such as Merrell Dow's cyclopentylamine and BCX-1812 (Figure 1). In spite of many elegant studies performed in this area,[2] there is still a need for designed analogues to obtain a better understanding of glycosidase functioning and also to prepare more potent and selective inhibitors. Therefore, new routes are required towards such attractive molecules.

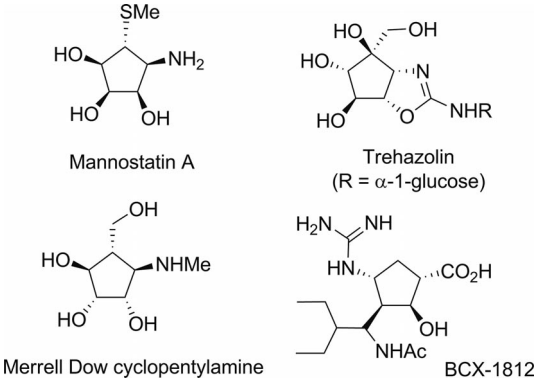
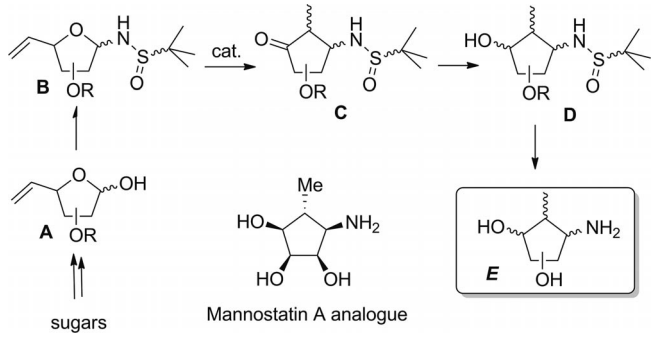



Figure 1. Some representative bioactive aminocyclopentitols.

Tandem isomerization–aldolization[3,4] and tandem isomerization–Mannich reactions[5] have been successfully developed as new methodologies for C–C bond formation, and we have demonstrated recently that the latter reaction, combined with the use of chiral *N*-sulfinimines,[6] was opening efficient routes to optically pure β-aminoketones and β-amino alcohols.[7] The goal of this communication is to demonstrate that a similar process, in the intramolecular version, is a short and efficient approach to new aminocyclopentitols. We have applied this methodology to the enantiosynthesis of an analogue of mannostatin A, as well as isomers of known fucosidase and glycosidase inhibitors.

The general strategy is indicated in Scheme 1. *N*-Protected derivatives **B** could be obtained from vinylic lactols **A**, themselves easily prepared from sugars.[8] By analogy with our previous work with lactols,[4] it was anticipated that an intramolecular tandem isomerization–Mannich reaction could occur to afford amino-protected cyclopentanone intermediate **C**. Then, simple reduction and deprotection steps should give target molecules **E**. The choice of the *tert*-butanesulfinyl protecting group was based upon the




Scheme 1. General strategy towards aminocyclopentitols and the first target, a mannostatin A analogue.

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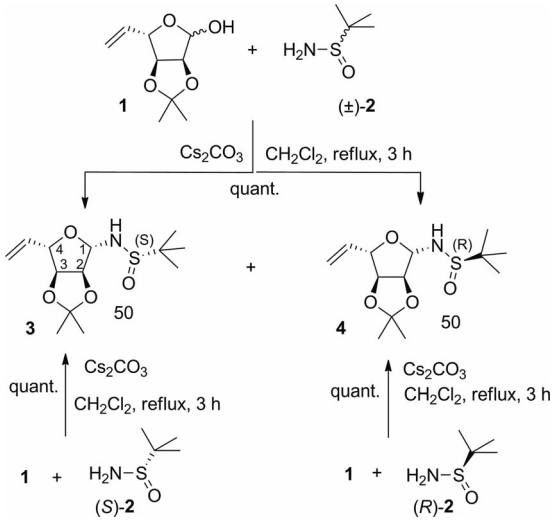
great advantages observed previously with respect to high stability under our transition-metal-catalyzed reaction conditions and complete stereocontrol.[6,7]

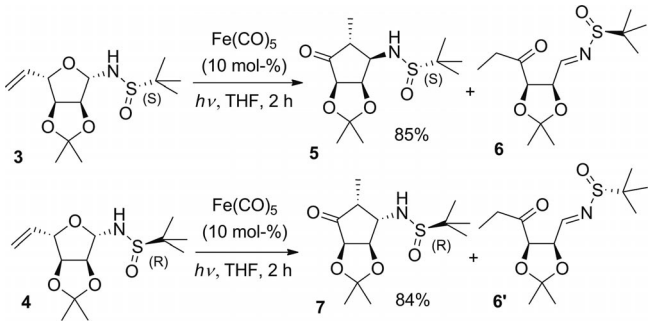
## Results and Discussion

Lactol **1** was easily prepared in three steps and 55% overall yield from D-ribose by following a literature procedure.[8] Condensation of **1** with racemic *N*-*tert*-butanesulfinamide (±)-**2** afforded, in quantitative yield, a 1:1 mixture of sulfinamides **3**/**4**, which were easily separated by chromatography. On the other hand, reactions were performed with each enantiomer of starting sulfinamide independently: we observed that the (*S*)-**2** enantiomer yielded only **3**, whereas diastereoisomer **4** was obtained quantitatively from the (*R*)-**2** enantiomer. Therefore, this condensation was stereospecific and was determined by the configuration of the starting sulfinamide (Scheme 2). The structures of derivatives **3** and **4** were established from the NMR spectroscopic data through small *trans* $^3J_{1,2}$ and $^3J_{3,4}$ (0.3–3.8 Hz) values observed for the protons of the tetrahydrofuran rings.




Scheme 2. Synthesis of sulfinamides **3** and **4**.

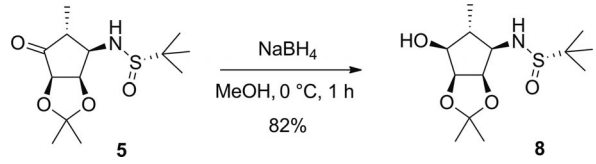
The tandem isomerization–Mannich reaction was successfully performed by using $Fe(CO)_5$ as the catalyst[9,10] with full stereocontrol (Scheme 3).




Scheme 3. Tandem isomerization–Mannich from **3** and **4**.

Starting from isomer **3**, the reaction gave cyclopentanone **5** in excellent yield, with a small amount (14%) of sulfinylimine **6**. On the other hand, reaction with sulfinamide **4** gave ketone **7**, with imine **6′** (14%).

The stereochemistry of these compounds was established by NMR spectroscopy and by correlation with X-ray analysis after the next step. Then, the reduction was performed on each stereoisomer independently: reaction of **5** with $NaBH_4$ was fully stereocontrolled, affording exclusively **8** in 82% isolated yield (Scheme 4). The stereochemistry of this alcohol was established by NMR spectroscopy and confirmed by X-ray crystallography (Figure 2).[11] As expected, the reduction occurred only from the face opposite to the two bulky substituents (acetonide and sulfinamide).




Scheme 4. Reduction of ketone **5**.

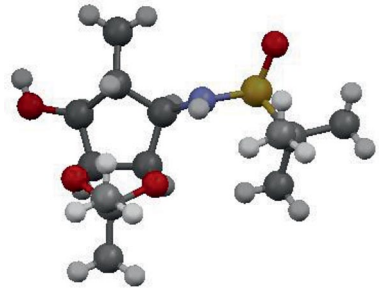


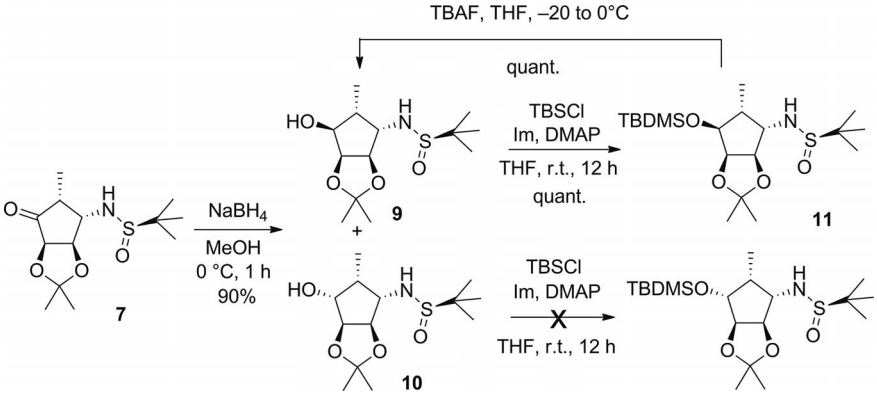
Figure 2. X-ray diffraction analysis of alcohol **8**.

On the other hand, reduction of ketone **7** afforded, in 90% overall yield and a 30:70 ratio, a mixture of alcohols **9**/**10**, which could not be separated by silica gel chromatography. However, isolation of both compounds in pure form was possible by a selective protection–deprotection strategy (Scheme 5). Upon reaction of the crude mixture of **9**/**10** with TBSCl (*tert*-butyldimethylsilyl chloride), imidazole, and 4-dimethylaminopyridine, only isomer **9** was protected as silyl ether **11** and alcohol **10** was recovered. After separation of **10** and **11** by chromatography, deprotection of silyl ether **11** afforded pure alcohol **9** in very good yield.

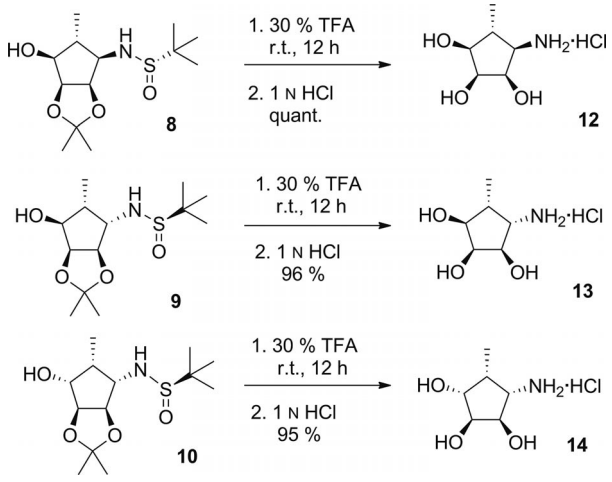
The last step in the synthetic scheme was deprotection of these derivatives. It was performed in a one-pot process by reaction first with trifluoroacetic acid overnight at room temperature, followed by reaction with HCl, affording desired target molecules **12**–**14** in excellent yields (Scheme 6).

These aminocyclopentitols appear to be of interest for biological studies and especially derivative **12**, which is a new analogue of mannostatin A. In-depth studies by Booms et al. have shown that the thioether-containing hydrophobic pocket was, at least in part, responsible for the better activity of mannostatin A.[12] Therefore, it will be very interesting to evaluate analogue **12** (with a Me group), as well as related compounds with various $CH_2R$ groups in




Scheme 5. Reduction of ketone **7** and isolation of alcohols **9** and **10**.




Scheme 6. Preparation of aminocyclitols **12**–**14**.

this position, derivatives which should be accessible through this strategy.

On the other hand, compounds **13** and **14** appear to be of biological interest, as they are isomers of a series of aminocyclitols prepared by other routes and active as fucosidase (i.e., **15**, **16**) and glycosidase (i.e., **17**) inhibitors (Figure 3).[2k,2l,13]

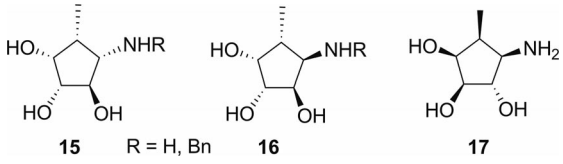



Figure 3. Representative examples of fucosidase inhibitors (i.e., **15** and **16**) and a glucosidase inhibitor (i.e., **17**).

## Conclusions

We have developed a new route to aminocyclopentitols. The tandem isomerization–Mannich reaction works efficiently under ironcarbonyl catalysis, with full stereocontrol by the *N*-*tert*-butanesulfinamide component. Development of this methodology is under active study in our group, and aminocyclopentitols obtained by this route will be of much use for structure–activity relationships in glycosidase inhibition.

## Experimental Section

**Tandem Isomerization–Mannich Reaction:** To a solution of **3** (125 mg, 0.6 mmol) in anhydrous THF (10 mL) was added $Fe(CO)_5$ (16 μL, 0.12 mmol, 10 mol-%). The mixture was irradiated with a Philip HPK 125 lamp for 1.5 h. The solvent was removed under reduced pressure, and the residue was filtered on silica gel ($Et_2O$). After concentration, the residue was purified by chromatography on silica gel (pentane/EtOAc, 1:1) to afford **5** (176 mg, 85% overall yield) and isomerized product **6** (29 mg, 14%).

**Representative Procedure for the Synthesis of Aminocyclitols:** A solution of 30% trifluoroacetic acid (1 mL) was added to compound **8** (20 mg, 0.106 mmol). The reaction mixture was stirred under an atmosphere of nitrogen overnight at room temperature and then extracted with pentane (3 × 5 mL) to remove the byproducts. A few drops of 1 N HCl were added, and the aqueous phase was co-evaporated in vacuo with toluene to afford hydrochloride **12** as a viscous orange oil (19 mg, quantitative).

**Supporting Information** (see footnote on the first page of this article): Full experimental procedures and characterization of compounds.

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[11] CCDC-824977 (for **8**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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