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Synthesis of (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols

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Abstract—Synthesis of (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols has been established starting from 2-benzyloxymethylpyrrolidin-2-one framework, which is derived from commercially available *trans*-(2*S*,4*R*)-4-hydroxyproline. The single diastereomer having a trans–cis relative configuration with C_2 and C_3 and C_3 and C_4 is constructed in two one-pot functional group transformations of Grignard addition/dehydration and epoxidation/isomerization as the key steps in moderate yield.

1. Introduction

Based on the structural framework of *trans*-(2*S*,4*R*)-4-hydroxyproline, it possesses three functional groups that can be easily modified and they are 1-amino, 2-carboxylate and 4-hydroxy groups.[1] The skeleton represents the significant feature for producing a series of different carbon frameworks such as monocycles (pyrrole,[2a] pyrrolidine,[2b,c,l] piperidine[2d] and azanucleoside[2e]), fused or bridged bicycles (pyrrolizidine[2f] or azabicycles[2g,h,m]), polycycles,[2i–k,n] macrocycle,[2o] etc. using an efficient modification technique.

Recently, we have introduced a facile and straightforward approach toward monocyclic pyrrolidine (anisomycin)[2l] and piperidine (α-conhydrine),[2m] bicyclic bridged 7-azabicyclo[2.2.1]heptane (epibatidine)[2n] and pyrrolophane (streptorubin B core),[2o] bicyclic fused hexahydro-1*H*-indol-3-one (pancracine)[2p] and acyclic γ-amino acid (statin and vigabatrin®)[2q,r] skeleton system via some easy functional group transformations, intramolecular basic alkylation, acidic aldol condensation, ring-closing metathesis and regioselective Baeyer–Villiger oxidation of different 2-substituted pyrrolidin-4-one framework employing *trans*-(2*S*,4*R*)-4-hydroxyproline as the starting material.

To demonstrate the synthetic utility of our methodology and explore the application to the synthesis of 2-substituted pyrrolidin-4-one, synthetic studies toward (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols were investigated (Fig. 1). Our interest in synthesizing 4-aryl-3-hydroxyprolinol (4-aryl-3-hydroxy-2-hydroxymethylpyrrolidine) skeleton was piqued on the different biological properties and because it is with the motif of 3-hydroxyl group and is a key intermediate for preparing many important skeletons of substituted piperidines and prolines.[3] Prolinol is an α-aminoalcohol with a unique nature inducing specific electronic and geometric features. The presence of such a ring in the chemical structure restricts conformational flexibility, which may efficiently modify binding affinity to its target. In addition, this peptidomimetic compound is expected to be more stable to hydrolysis by metabolic enzymes.

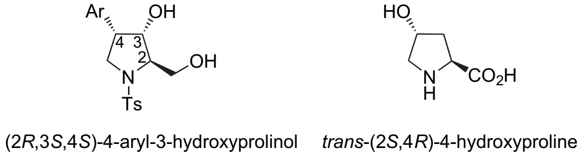

Figure 1. Structures of (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinol and *trans*-(2*S*,4*R*)-4-hydroxyproline.

2. Results and discussion

2.1. Retrosynthetic analysis of (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols 1a–d

We now wish to report an easy and straightforward synthesis of (2*S*)-2-benzyloxymethylpyrrolidin-4-one **3** leading to four (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols **1a–d** by two remarkable one-pot transformations as shown in Scheme 1. One

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Keywords: (2*R*,3*S*,4*S*)-4-Aryl-3-hydroxyprolinols; *trans*-(2*S*,4*R*)-4-Hydroxyproline; One-pot reaction; Grignard addition/dehydration; Epoxidation/isomerization.

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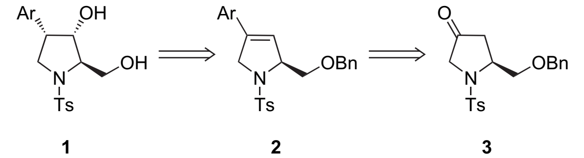
is the access to produce (2*S*)-4-aryl-2-benzyloxymethyl-2,5-dihydropyrroles **2a–d** by the Grignard addition of compound **3** and subsequent boron trifluoride etherate mediated dehydration of the resulting tertiary alcohols. The other is a specific step from olefins **2a–d** to diols **1a–d** by stereochemical epoxidation and followed by boron trifluoride etherate mediated isomerization of the resulting epoxides.

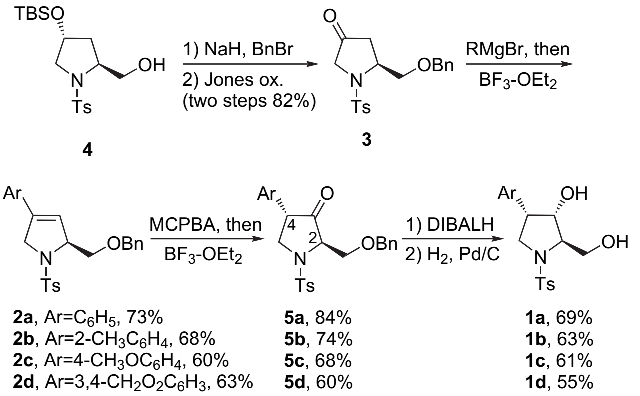


a, Ar=C_6H_5; **b**, Ar=2-$CH_3C_6H_4$; **c**, Ar=2-$CH_3OC_6H_4$; **d**, Ar=3,4-$CH_2O_2C_6H_3$

Scheme 1. Retrosynthetic analysis of (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols **1a–d**.

2.2. Synthesis of (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols 1a–d

In a previous report,[2m–q] synthesis of prolinol **4** from *trans*-(2*S*,4*R*)-4-hydroxyproline provided a 90% overall yield with purification done only once via a facile four-step reaction. As shown in Scheme 2, prolinol **4** was first transformed into ketone **3** (82% yield in two steps) by *O*-benzylation and Jones oxidation under the standard conditions. With enough amounts of ketone **3**, conversion of ketone **3** into olefins **2a–d** was further examined.



Scheme 2. Synthetic approach toward (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols **1a–d**.

Treatment of ketone **3** with different arylmagnesium bromide reagents (a, Ar=C_6H_5; b, Ar=2-$CH_3C_6H_4$; c, Ar=4-$CH_3OC_6H_4$; d, Ar=3,4-$CH_2O_2C_6H_3$) in tetrahydrofuran provided a pair of diastereoisomers (ca. 1:1 ratio) without any induction onto the stereoselectivity.[4a] Following this similar approach, attempts to form a sole tertiary alcohol under a variety of conditions (prolonged reaction time, diverse temperature, different solvents) were unsuccessful.[4]

With these results in hand, the direct one-pot conversion for the reaction of ketone **3** with four arylmagnesium bromide reagents and subsequent dehydration of the resulting tertiary alcohols with boron trifluoride etherate yielded compounds **2a–d** in 60–73% overall yield. During the one-pot process, 4-aryl-2-benzyloxymethyl-2,3-dihydropyrrole framework was not observed. In the other way, one-pot reaction of ketone **3** with methylmagnesium bromide and followed by dehydration was also examined. Treatment of 4-hydroxy-4-methyl-2-benzyloxymethylpyrrolidine yielded 4-methyl-2-benzyloxymethyl-2,5-dihydropyrrole in trace amounts under the acidic conditions (e.g., boron trifluoride etherate, aluminum chloride and Dean–Stark distillation). Based on these results, we envisioned that aryl group is an important substituent, which easily provides a stable benzylic cation in the dehydration process. However, 4-methyl-2-benzyloxymethyl-2,5-dihydropyrrole was carried out in 34% yield by the basic dehydration of this tertiary alcohol with mesyl chloride and pyridine.

To investigate the relative stereochemistry of diols **1a–d** at C_2 and C_3 and C_3 and C_4 positions, epoxidation of olefins **2a–d** and isomerization of the resulting epoxides **2aa–da** were studied in the next stage. Epoxidation of model substrate **2a** with *m*-chloroperoxybenzoic acid afforded a sole epoxide **2aa** with three contiguous asymmetric centers in 92% yield. The structural stereochemistry of epoxide **2aa** was determined by single-crystal X-ray analysis (Diagram 1).[5] According to the provided epoxide **2aa**, we envisioned that stereoselective epoxidation of olefin **2a** was strongly affected by the steric hindrance of 2-benzyloxymethyl group.[6] Both 4-phenyl and 2-benzyloxymethyl groups in the structure of epoxide **2aa** could be arranged as *cis* configuration. Next, ketone **5a** was afforded by the selective isomerization of trisubstituted epoxide **2aa** via hydride shift in 91% yield.[7] Therefore, the stereochemical assignment of ketone **5a** at C_2 and C_4 centers was made the trans configuration.

For the epoxidation of olefins **2c–d** with electron-donating groups, the desired epoxides **2ca–da** could not be obtained and complex products were isolated during silica gel chromatography. With the previous experiences in mind,[8] we envisioned that the problem was solved by the one-pot reaction. Therefore, ketones **5a–d** were yielded via the one-pot reaction of olefins **2a–d** with the combination of *m*-chloroperoxybenzoic acid and followed by boron trifluoride etherate in 60–84% overall yield. Ketones **5a–d** must be purified by recrystallization from dichloromethane and methanol because the generated racemic mixture was observed by the epimerization of C_2 or C_4 position during silica gel-mediated chromatographic purification.

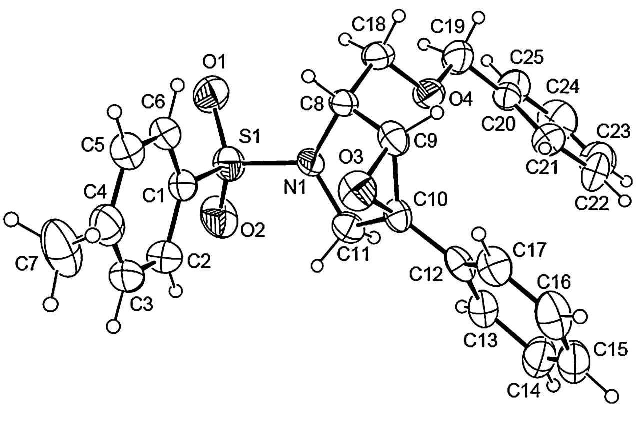


Diagram 1. X-ray crystallography of epoxide **2aa**.