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# An Efficient Asymmetric Synthesis of (R)-3-Amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one†

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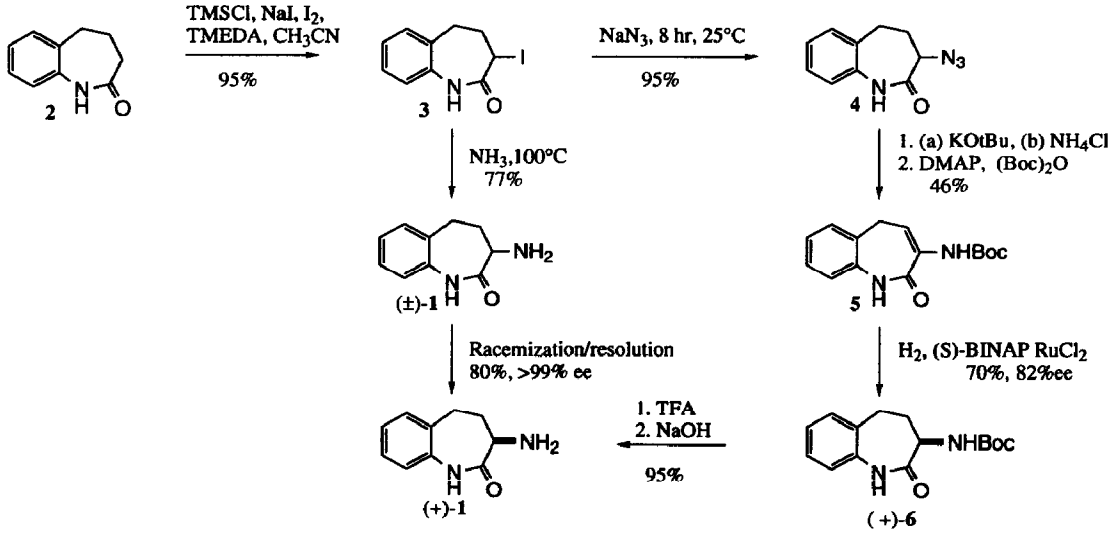
***Abstract:*** *Two approaches for the asymmetric preparation of (-)- or (+)- α-aminobenzlactam 1 are described. One route is based on the asymmetric hydrogenation of enamide 5 and the other on the racemization/resolution of (±)- 1.*

3-Amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one, or α-aminobenzlactam, (±)-**1** is an important structural feature for angiotensin converting enzyme (ACE) inhibitors[1] and for growth hormone secretagogues.[2] A previous synthesis[3] of (+)-**1** required a resolution to obtain the (R)-enantiomer. Herein we describe the first enantioselective synthesis of (+)- or (-)-**1**. In designing a practical asymmetric synthesis of (+)-**1** we chose a dual approach. One route is based on the unprecendented asymmetric hydrogenation of enamide **5** and a second, more direct method utilizes a racemization/resolution of α-aminobenzlactam (±)-**1** (Scheme 1). Both of these approaches rely on an efficient preparation of the key intermediate, α-iodobenzlactam **3**.

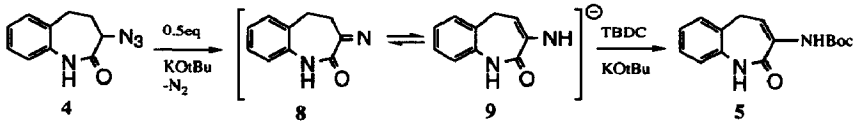



Scheme 1

Since both methods incorporate iodobenzlactam **3** as the key intermediate, an efficient and practical preparation was necessary. Our starting material was the known benzlactam **2**,[4] prepared from α-tetralone using Eaton's[5] modification of the Beckmann rearrangement of the corresponding oxime.

Formation of the α-monochloride or bromide of benzlactam **2** has been accomplished by bis-halogenation, followed by selective removal of one halogen by catalytic hydrogenation.[3] However, we decided to use a modification of the reaction recently developed in these laboratories by A.O. King et.al.,[6] which generates the α-iodobenzlactam directly. The more reactive iodide was preferred over the other halogens for displacement by ammonia or sodium azide. Treatment of **2** with TMSCl, NaI, $I_2$ and TMEDA in $CH_3CN$ at -15°C generated the α-iodobenzlactam **3** in 95% yield.[7]

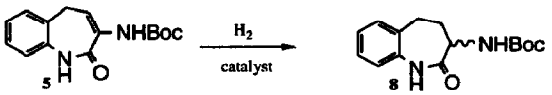
With an optimized process for the formation of **3** in hand, investigations were focused on the generation of enamide **5** from α-azidobenzlactam **4**. The latter was prepared in 91% yield by reaction of **4** with 1.5 eq. of $NaN_3$ in DMF at ambient temperature for 8 h. Treatment of the azide with potassium t-butoxide (KOtBu) generated $N_2$ and a mixture of imine/enamine intermediates **8/9**, which were trapped *in situ* with t-butyldicarbonate (TBDC) to give enamide **5** in low and variable yield (see Scheme 2).[8] After extensive variation of base, temperature, and trapping agent, the optimized conditions for preparation of enamide **5** were deprotonation of α-azidobenzlactam **4** with 0.5 eq. of KOtBu, followed by quenching with saturated $NH_4Cl$. The isolated enamine was allowed to react with TBDC and DMAP to give enamide **5** in 46% overall yield from **4**.




Scheme 2

Asymmetric hydrogenations of endocyclic lactam enamides, with rhodium or ruthenium catalysts have not been reported in the literature.[9] Results of a systematic study of the asymmetric hydrogenation of enamide **5** with chiral rhodium and ruthenium catalysts are listed in Table 1. High enantiomeric excess (82% ee) and conversion occurred with Noyori's ruthenium catalysts[10] [(S)-BINAP $RuCl_2$ and (R)-BINAP $RuCl_2$] (entries 2 and 3), but only low induction (5-20% ee) and <10% conversion occurred with the rhodium catalysts.[11]

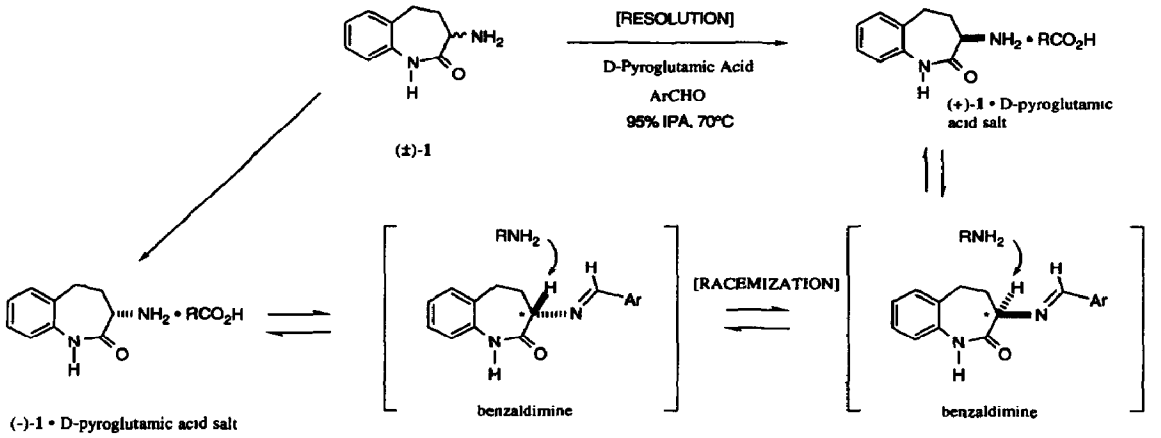
Table 1: Asymmetric Hydrogenation of Enamide 5




| Entry | Catalyst[a] | Solvent | Psi | °C | R/S ratio[b] | % Conversion[c] |
|---|---|---|---|---|---|---|
| 1 | (R)BINAP $RuCl_2$ | EtOH | 50 | 60 | 18:82 | 56 |
| 2 | (R)BINAP $RuCl_2$ | MeOH | 40 | 60 | 9:91 | 80 |
| 3 | (S)BINAP $RuCl_2$ | EtOH | 50 | 60 | 82:18 | 56 |

[a]The ruthenium catalysts were isolated according to the procedure described by S. A. King, et.al.[12] [b]Enantiomeric ratios were determined by chiral HPLC, Chiracel (+)OD column, 210 nm, eluting with 95:5 hexane:isopropanol solution. [c]Determined by HPLC, Dupont Zorbax C-8 column, 210 nm, eluting with mixture of 0.1% aqueous $H_3PO_4$ and $CH_3CN$.

Also, the racemization/resolution of (±)-1 was investigated. The α-aminobenzlactam (±)-1 was isolated in 77% yield by the aminolysis of α-iodobenzlactam 3 (Scheme 1). After screening several chiral acids , D-pyroglutamic acid[13] was used in the racemization-resolution experiments (Scheme 3). The initial racemization-resolution[14] of (±)-1 with D-pyroglutamic acid and 3,5-dichlorosalicylaldehyde (3.0 mol%,[15] 95% aqueous isopropanol, 70°C, 120 h) gave the desired (R)-(+)-1•D-pyroglutamic acid salt in 88% yield with 96% ee. Substitution of 5-nitrosalicylaldehyde as the catalyst under the same conditions gave the desired (R)-(+)-1•D-pyroglutamic acid salt in 88% yield with 98% ee after only 48 h. This markedly accelerated rate of racemization presumably is the result of the increased acidity of the $C_3$ proton of the derived 5-nitrobenzaldimine (Scheme 3).




Scheme 3

The enantiomeric purity of the isolated (R)-α-aminobenzlactam (+)-1 salt (98% ee) could be upgraded by slurrying in 90:10 acetonitrile:water at 70-73°C to give an isolated salt with 99.8% ee in 95% yield. The conversion of the (+)-1•D-pyroglutamic acid salt to free base (+)-1 was accomplished by addition of concentrated ammonium hydroxide to an aqueous solution of the salt, followed by extraction with methylene chloride and vacuum concentration. The free base (+)-1 was obtained in 96 % yield with 99.8 % ee. The overall yield of the free amine (+)-1 from (±)-1 was 80%.

In sumary, two efficient methods for the asymmetric preparation of either enantiomer of α-aminobenzlactam 1 from α-iodobenzlactam have been presented: an unprecedented asymmetric catalytic hydrogenation of enamide 5 and a more direct approach utilizing a racemization/resolution of α-aminobenzlactam (±)-1.

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† Dedicated to the memory of William F. Benning.

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