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Chemoenzymatic synthesis of (3*S*,4*S*)- and (3*R*,4*R*)-3-methoxy-4-methylaminopyrrolidine

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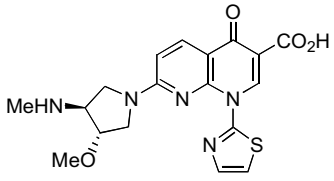
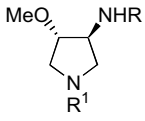
Abstract—Facile chemoenzymatic enantioselective synthesis of (3*S*,4*S*)-3-methoxy-4-methylaminopyrrolidine, a key intermediate for a new quinolone antitumor compound AG-7352 has been described. This methodology illustrates the preparation of 3-azido-1-benzyloxycarbonyl-4-hydroxypyrrolidine starting from diallylamine via 1-benzyloxycarbonyl-3-pyrroline obtained by ring-closing metathesis (RCM) employing Grubbs' catalyst. Enzymatic transesterification employing PS-C lipase gave (3*S*,4*S*)-3-azido-1-benzyloxycarbonyl-4-hydroxypyrrolidine in >99% ee, which upon methylation of the hydroxyl group followed by sequential reactions gave the desired intermediates, (3*S*,4*S*)-1-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylamino-4-methoxypyrrolidine.

A large number of synthetic and naturally occurring biologically important compounds contain chiral pyrrolidines as subunits in their structures.[1] Tsuzuki and co-workers[2,3] have recently developed a novel antitumor agent quinolone framework that has a 3-methoxy-4-methylaminopyrrolidine group **2a** at the C-7 position (AG-7352, **1**). This compound has been claimed to possess equal or superior antitumor activity to those of cisplatin and etoposide against human breast, ovarian, and colon cancers implanted in nude mice.[4] Some quinolone related compounds show antitumor activity with inhibition of eukaryotic topoisomerase II.[5] 3-Methoxy-4-methylaminopyrrolidine **2a** is a key intermediate for the synthesis of **1** and it is also an intermediate for related biologically important heterocyclic compounds.[6,7] Recently, a structure activity relationship study carried out for 7-substituted 1,4-dihydro-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acids has shown that the stereochemistry of the 7-substituted pyrrolidine group effects the in vitro and in vivo cytotoxicity of these compounds,[8] thus illustrating the importance of the preparation of this pyrrolidine intermediate in optically pure form. There are very few methods that have been reported for the stereospecific synthesis of this biologically active pyrrolidine intermediate. These methods involve either a chiron approach[2,9] or an optical resolution of a racemate.[3] In view of our interest for the development of chemoenzymatic methodologies, it was considered of interest to develop a chemoenzymatic route for the preparation of the optically active precursor **2b**. Herein, we wish to report an efficient chemoenzymatic synthesis of **2b** starting from diallylamine involving ring-closing metathesis and lipase mediated resolution.



AG-7352 (1)



(*S*,*S*)

2a R=Me, R^1=H
2b R= R^1=Boc

In the present synthetic strategy, commercially available diallylamine **3** was employed as the starting material for the construction of the pyrrolidine ring. The amine functionality of compound **3** was protected with CbzCl before ring-closing metathesis employing Grubbs' catalyst to give *N*-Cbz-3-pyrroline **5**. The epoxide **6** was

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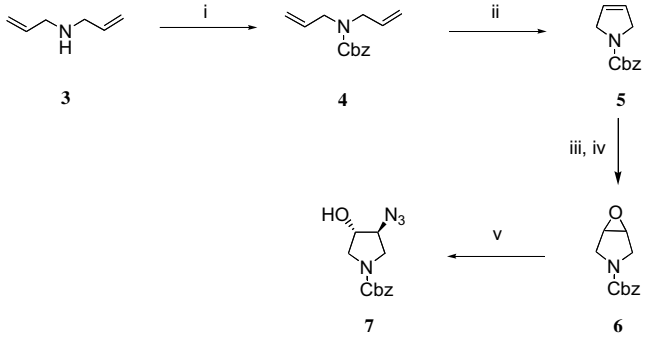
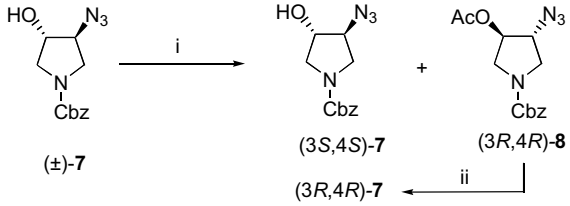


Scheme 1. Reagents and conditions: (i) CbzCl, Et_3N, CH_2Cl_2, rt, 10 h, 98%; (ii) $(Pcy_2)_2Cl_2Ru{=}CHph$, CH_2Cl_2, rt, 6 h, 96%; (iii) NBS, DMSO–H_2O, rt, 2 h, 89%; (iv) 1 N NaOH, rt, 1 h, 76%; (v) NaN_3, 1,4-dioxane–H_2O, reflux, 12 h, 85%.

obtained from **5** via its bromohydrin and epoxide **6** upon treatment with NaN_3 yielded the required intermediate (±)-*trans*-3-azido-1-Cbz-4-hydroxypyrrolidine **7** (Scheme 1). In view of our interest in enzyme mediated kinetic resolutions of chiral building blocks,[10] we carried out the lipase mediated resolution of compound (±)-**7**. A number of lipases from different sources[11] were examined for this process and it was observed that lipases from *Pseudomonas cepacia* particularly in their immobilized forms, that is, PS-C (lipase immobilized on ceramic particles) and PS-D (lipase immobilized on diatomaceous earth) gave interesting results with respect to conversion and enantioselectivity. Moreover, the effect of various solvents was also investigated for this transesterification process employing PS-C lipase.[12] Diisopropyl ether provided suitable conversion with high enantioselectivity employing vinyl acetate as an acylating agent (Scheme 2). The lipase catalyzed transesterification[13] of (±)-*trans*-3-azido-1-Cbz-4-hydroxypyrrolidine **7** using PS-C lipase and vinyl acetate in diisopropyl ether afforded (3*S*,4*S*)-**7** (46% yield, >99% ee)[14] and (3*R*,4*R*)-**8** (52% yield, 81% ee).[15] The deacetylation of (3*R*,4*R*)-**8** using anhydrous K_2CO_3 in methanol gave (3*R*,4*R*)-**7** with 81% ee.[16]

The enantiomerically enriched (3*S*,4*S*)-3-azido-1-Cbz-4-hydroxypyrrolidine **7** obtained by the lipase mediated kinetic resolution of (±)-**7** was converted to its methyl



Scheme 2. Reagents and conditions: (i) lipase PS-C, vinyl acetate, diisopropylether, 10 h; (ii) K_2CO_3, methanol, 2 h.

ether (3*S*,4*S*)-**9** using MeI/NaH. The pyrrolidine azide (3*S*,4*S*)-**9** was reduced to its amine under mild conditions employing PPh_3 in THF–H_2O followed by protection with $(Boc)_2O$ to give (3*S*,4*S*)-**10**. Compound (3*S*,4*S*)-**10** upon Cbz deprotection under extremely mild conditions employing poly(methylhydrosiloxane) (PMHS) over 10% Pd/C in ethanol followed by treatment with $(Boc)_2O$ gave the required product (3*S*,4*S*)-**2b** with >99% ee. The other enantiomer (3*R*,4*R*)-**7** obtained by employing the same reaction sequence was converted to (3*R*,4*R*)-**2b** with 81% ee (Scheme 3). The absolute configurations of the compounds have been confirmed by comparison of their rotation values with those previously reported.[17]

In summary, an efficient chemoenzymatic methodology has been developed for the preparation of (3*S*,4*S*)-**2b** a key intermediate required for the synthesis of the novel quinolone antitumor agent AG-7352 **1**. This protocol provides excellent enantiomeric excess through lipase PS-C mediated kinetic resolution. Moreover this method utilizes a simple and inexpensive starting material, diallylamine for building the pyrrolidine ring. Additionally this method describes the synthesis of both the enantiomers of this key intermediate **2b** in high degree of enantiopurity.

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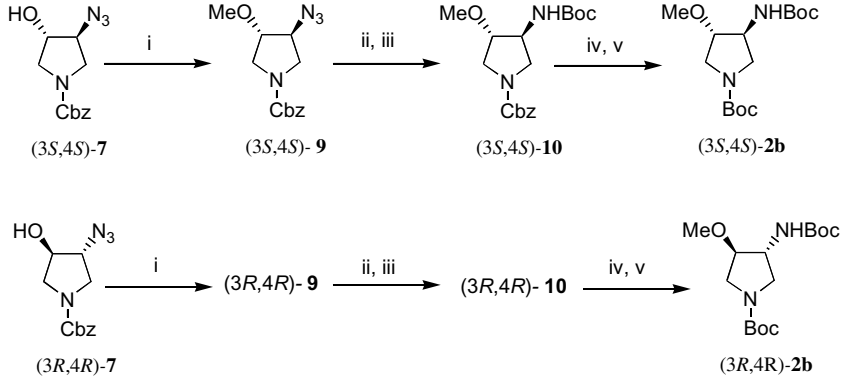

Scheme 3. Reagents and conditions: (i) MeI, NaH, DMF, rt, 6 h, 72%; (ii) PPh_3, THF–H_2O, rt, 2 h; (iii) $(Boc)_2O$, Et_3N, rt, 6 h, 93%; (iv) PHMS, 10% Pd/C, EtOH; (v) $(Boc)_2O$, Et_3N, rt, 8 h, 95%.

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11. Different lipases were screened, among them *Pseudomonas cepacia* (PS-C) gives good enantioselectivity within 10 h compared to PS-D. *Pseudomonas cepacia* lipase (PS), *Pseudomonas fluorescens* (AK-20), Lipozyme immobilized from *Mucor miehei*, *Candida rugosa* lipase gave lower enantioselectivities. There were no significant conversions by employing lipases from *Candida antartica*, *Porcine pancreas*, and *Candida cylindracea*.
12. A number of solvents such as diisopropyl ether, toluene, THF, *tert*-butyl methyl ether, and hexane were examined for this protocol. It was observed that diisopropyl ether was efficient for this lipase mediated resolution, whereas toluene takes longer (2 days) reaction times and gave comparatively low enantioselectivity. The results employing THF, *tert*-butyl methyl ether, and hexane were not satisfactory.
13. General procedure for lipase mediated transesterification: To a solution of (±)-*trans*-3-azido-1-Cbz-4-hydroxypyrrolidine **7** (1 mmol) in diisopropyl ether (10 mL) was added lipase PS-C (1 equiv w/w), vinyl acetate (6 mmol). The suspension was shaken at 150 rpm at 40 °C. The reaction mixture was monitored by chiral HPLC analysis until it reached about 50% conversion (10 h). The reaction was filtered and the filtrate was washed with water followed by brine. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography. The enantiopurity of the products (3*S*,4*S*)-**7** and (3*R*,4*R*)-**8** were determined by a chiral HPLC using Chiralcel OD column (hexane–isopropanol, 80:20) with 0.5 mL/min flow rate and compared with the corresponding racemic products.
14. Compound (3*S*,4*S*)-**7**: t_R = 15.49 min; $[\alpha]_D^{25}$ +14.3 (*c* 1.06, $CHCl_3$).
15. Compound (3*R*,4*R*)-**8**: t_{major} = 18.97, t_{minor} = 17.61 min; $[\alpha]_D^{25}$ −17.7 (*c* 1.02, $CHCl_3$).
16. Compound (3*R*,4*R*)-**7**: t_{major} = 19.19, t_{minor} = 15.49 min; $[\alpha]_D^{25}$ −10.6 (*c* 1.02, $CHCl_3$).
17. Spectral data for compounds (3*S*,4*S*)-**2b** and (3*R*,4*R*)-**2b**: Compound (3*S*,4*S*)-**2b**: $[\alpha]_D^{25}$ −18.7 (*c* 1.01, MeOH) {lit.[2] $[\alpha]_D^{25}$ −18.1 (*c* 1.08, MeOH)}. Compound (3*R*,4*R*)-**2b**: $[\alpha]_D^{25}$ +14.7 (*c* 1.1, MeOH); IR (neat): 3318, 2924, 1685, 1410, 1163 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.46 (18H, s), 3.2–3.46 (3H, m), 3.42 (3H, s), 3.64 (1H, dd, *J* = 5.5, 12 Hz), 3.75–3.84 (1H, m), 3.96–4.09 (1H, m), 4.69 (1H, br s); FABMS (*m*/*z*): 317 (M^++1).