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A short, simple and general approach for the synthesis of (3*S*,4*S*)-3-methoxy-4-methylamino pyrrolidine and (3*S*,4*R*)-3-methoxy-4-methylamino pyrrolidine☆

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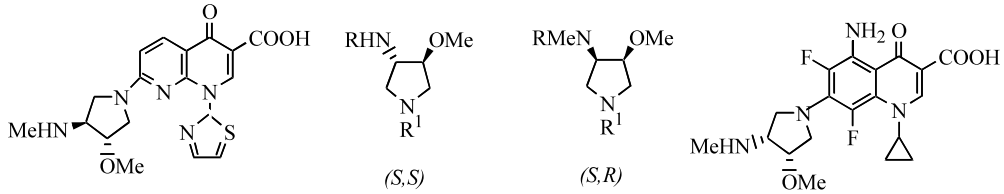
Abstract—A general and efficient stereoselective approach for the synthesis of (3*S*,4*S*) and (3*S*,4*R*)-3-methoxy-4-methylamino pyrrolidines, a part of the structure of AG-7352, a naphthyridine antitumor agent and quinoline antibacterial compounds has been described.

Biologically active chiral and non-racemic pyrrolidines are commonly found in subunits of natural and unnatural products.[1] Okada et al.[2,3] showed that a new series of quinoline compounds, e.g. **1a**, bearing a 3-methoxy-4-amino chiral pyrrolidine derivative at C-7 showed higher in vivo and in vitro antibacterial activity against gram +ve and gram –ve bacteria. The pyrrolidine skeleton possesses 3-methoxy-4-amino or 3-methoxy-4-methylamino groups both in *syn* and *anti* configurations. Tsuzuki et al.[4,5] also showed that (3*S*,4*S*)-3-methoxy-4-methylaminopyrrolidines attached to the naphthyridine ring at C-7 in AG-7352 **1**, a new type of antitumor agent, showed potent activity equal or superior to those of cisplatin and etopside.[6] The amino and hydroxy moieties in the *erythro* form are also present in a pyrrolidine containing balanol analogue,[7] which is a very effective inhibitor of Protein Kinase C (PKC). Hence these novel pyrrolidine moieties must contribute to the activity of the above compounds. Therefore, we undertook the synthesis of these 3,4-disubstituted pyrrolidines and developed a new general strategy for the preparation of both *syn* and *anti* compounds **3a** and **2a**. Although an approach[3] towards the synthesis of **3a** is known, it is racemic and the chiral pyrrolidine **3a** was obtained only after resolution. Also two approaches[4] are known for **2a** based on an S_N2 displacement reaction and chiral resolution from tartaric acid. Herein we present a short, stereoselective and general approach for both **2a** and **3a** starting from isoascorbic acid and ascorbic acid, respectively (Fig. 1).

Our approach to the synthesis of (*S*,*S*)-pyrrolidine **2b** is outlined in Scheme 1. D-Isoascorbic acid was converted into the diol **4** by the sequence of reactions reported earlier.[8] The primary alcohol was converted into its azide **6** via the tosylate using TsCl–Py and NaN_3 in



AG-7352 (+)1

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

3a R= H, R^1= H
3b R= R^1= Boc

1a

Figure 1.

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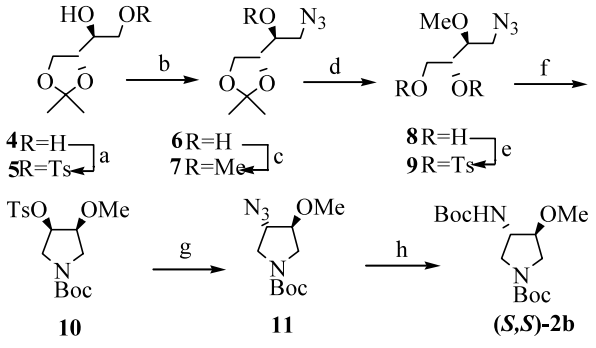
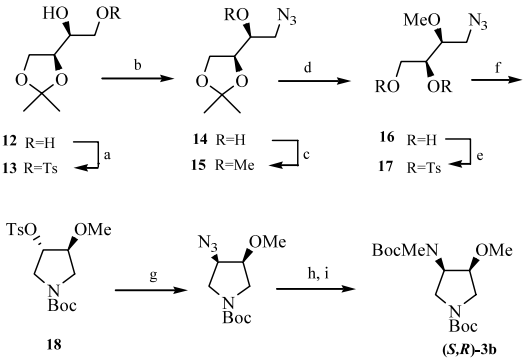


Scheme 1. *Reagents and conditions*: (a) *p*-TsCl, Py, 0°C, 12 h, 93%; (b) NaN_3, DMF, 80°C, 8 h, 96%; (c) NaH, MeI, DMF, 0°C–rt, 6 h, 91%; (d) PTSA (cat.), MeOH, rt, 10 h, 83%; (e) *p*-TsCl, Et_3N, DCM, rt, 24 h, 83%; (f) TPP, MeOH, reflux, 12 h then $(Boc)_2O$, Et_3N, THF, 14 h, 48%; (g) NaN_3, DMF, 80°C, 8 h, 84%; (h) Pd/C, H_2, EtOH, rt, 2 h, then Et_3N, $(Boc)_2O$, DCM, 96%.



Scheme 2. *Reagents and conditions*: (a) *p*-TsCl, Py, 0°C, 12 h, 89%; (b) NaN_3, DMF, 80°C, 8 h, 92%; (c) NaH, MeI, DMF, 0°C–rt, 6 h, 94%; (d) PTSA (cat.), MeOH, rt, 10 h, 83%; (e) *p*-TsCl, Et_3N, DCM, rt, 24 h, 87%; (f) TPP, MeOH, reflux, 12 h then $(Boc)_2O$, Et_3N, THF, 14 h, 52%; (g) NaN_3, DMF, 80°C, 3 days, 75%; (h) Pd/C, H_2, EtOH, rt, 2 h, then Et_3N, $(Boc)_2O$, DCM, 95%; (i) MeI, NaH, DMF, 0°C to rt, 2 h, 94%.

DMF. The azidoalcohol thus obtained was protected as the methylether using MeI/NaH to give compound **7**. Under acidic conditions (cat. amount of PTsA in MeOH) compound **7** underwent isopropylidine cleavage to furnish the diol **8**,[9] which was converted into ditosyl derivative **9** using TsCl/Et_3N. Reaction of compound **9** in TPP/MeOH at reflux resulted in azide reduction and regioselective cyclization to give the pyrrolidine derivative, which was subsequently Boc protected to give **10**.

Next, the tosyl group in compound **10** underwent S_N2 displacement with NaN_3 in DMF to furnish azide **11** which on further reduction with Pd/C, H_2 and protection with $(Boc)_2O$ afforded compound **2b** whose spectral and analytical data were in agreement with the reported values.[4] Compound **2b**, after *N*-methylation and Boc deprotection was coupled with the naphthyridine moiety to give AG-7352 **1**, which has been reported in the literature.[5]

Pyrrolidine **3b** was synthesized from L-ascorbic acid using the same strategy following the sequence of reactions described in Scheme 2. In this case conversion of compound **18** to its azide **19** required heating the reaction mixture for 3 days at 80°C. This may be due to steric hindrance resulting from the '*trans*' configuration in compound **18**. On treatment with Pd/C, H_2 the azide group in **19** was reduced to the amine which was protected as its Boc derivative and *N*-methylated to give **3b** whose spectral and analytical data were in agreement with the assigned structure. Compound **3b**, after Boc deprotection, was coupled with the quinoline moiety reported in the literature.[3]

In conclusion, an efficient and general approach for the synthesis of chiral pyrrolidines **2a** and **3a** has been developed. Thus, the above strategy should be useful in preparing different pyrrolidine analogues of therapeutic benefit.

Spectral data for some selected compounds:

Compound **2b**: $[\alpha]_D^{25} = -18.6$ (*c* 0.6, MeOH) [(lit.[4] $[\alpha]_D^{25} = -18.1$ (*c* 1.08, MeOH)]; IR (neat, cm^{-1}): 3318, 2924, 1688, 1414, 1168; ^1H NMR (200 MHz, $CDCl_3$): δ 1.46 (s, 18H), 3.21–3.44 (m, 3H), 3.41 (s, 3H), 3.61 (dd, 1H, $J = 5.5$ Hz, 12 Hz), 3.62–3.8 (m, 1H), 3.98–4.12 (m, 1H), 4.6 (bs, 1H); FABMS *m*/*z* 317 (M^++1).

Compound **3b**: $[\alpha]_D^{25} = +51.7$ (*c* 0.65, MeOH) [(lit.[3] $[\alpha]_D^{25} = +53.7$ (*c* 1.00, MeOH)]; IR (neat, cm^{-1}): 2931, 2358, 1695, 1404, 1366, 1156, 879, 757; ^1H NMR (300 MHz, $CDCl_3$): 1.48 (s, 9H), 1.49 (s, 9H), 2.89 (s, 3H), 3.32 (s, 3H), 3.36–3.61 (m, 4H), 3.9 (m, 1H), 4.6 (m, 1H). FABMS *m*/*z* 331 (M^++1).

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