Stereoselective synthesis of stable isotopomers of meso-2,6-diaminopimelic acid

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Introduction

Due to heavy use of antibiotics in our modern society, bacteria developed many resistance mechanisms. It is only a matter of time before the latest discovered antibiotic becomes obsolete[1-2,3,4]. In that regard scientists continuously need to find new targets to design new antibiotics.

meso-2,6-Diaminopimelic acid or m-Apm, is a diamino diacid only found in bacterial peptidoglycan. It is essential to a large proportion of bacterial species, mostly Gram negative bacteria, allowing reticulation between glycans strands (Figure 1).

Bacteria cannot survive without peptidoglycan. This macromolecule has a structural role and allows them to resist to their high inner osmotic pressure. Therefore peptidoglycan metabolism is a target of choice in antibiotics development.

In this work, we synthesized stable isotopomers (15C, and 13C) of m-Apm to provide tools that will help biologists to study peptidoglycan metabolism.

Results

1. Strategy

The key intermediate of our strategy is pictured in Figure 2. This family of compounds can be obtained by cross metathesis (CM) between vinylglycine (Vgl) and algylicine (Agl) synths[5].

Figure 2 | Key intermediate.

Deuteration can be introduced in the synthesis after the CM step by catalytic reduction of the alkene bond. The cheapest way to introduce carbon-13 is to synthesize a 13C-Agl from glycine-1-13C (1546/6).

2. Allylglycine synths synthesis

(5)-Allylglycine synths 4a and 4b were obtained by alkylation of N-(diphenylmethylene)glycine tert-butyl ester 2 (a Schift base, commercially available) using chiral phase transfer catalysis (Figure 3). The cinchonidine based catalyst 2 was synthesized in our lab[5].

Figure 3 | 13C-Allylglycines synths. i) CH2=CH2Br, KOH (50/1 wt%), toluene, CHCl3, -20°C. ii) citric acid (10/1 wt%), THF, 13C-allylglycine 4a, toluene, 0 °C (98%).

Enantiomeric excess are very satisfying (4a 97% ee, 4b 90% ee, measured on chiral Daicel OD-H HPLC column). Once (S)-Schiff base 6 prepared from glycine-1-13C 5 (Figure 4), the same alkylation process was applied to yield protected 13C-Algl 8. Vinylglycine synths 9 (Figure 5) was also synthesized in our lab[6] (85%, 3 steps, ee = 98%).

Figure 4 | 13C-Allylglycine synthesis. i) Cbz-Cl, NaOH (aq), toluene, 0°C → rt; BuO-tol, DCC, DMAP, CH2Cl2, H2 (6 bar), Pd/C (10%/w, dry), HCl, MeOH, Ph4P-C=NH, CH2Cl2, MgSO4, H2O; ii) CH2=CH2Br, KOH (50%/w, aq), toluene, CH2Cl2, -20°C, citric acid (10%/w, THF, Fmoc-tosylate, THF, H2O (51%, 7 steps).

3. Cross-metatheses and PG removal

Protecting groups (PG) of 10 were chosen to suit future solid phase peptide synthesis. In this case, CM yields were very satisfying. Unfortunately the Fmoc removal proved to be the most challenging step of these syntheses.

Figure 5 | 13C-m-Apm synths. i) Grubs 2nd gen. cat. 10 mol%, CH2Cl2, reflux, N2 (yield = 66%). ii) HCl (2 M, aq), 1,4-dioxane, reflux ; H2 (6 bar), Pd, HCl, MeOH (35%, 2 steps).

In this study, we prepared 3 different isotopomers of m-Apm by cross metathesis: natural m-Apm (18%), 6 steps), 13C-Apm (18%), 6 steps) and 13C-15C-Apm (12%, 10 steps).

This last synthesis still needs some optimization in the last step. These compounds will be analyzed in HPLC to determine their diastereomeric excesses but no evidence of racemization was observed in NMR and HPLC analyses. Shortly, we will use a similar strategy to produce tributyl 13C-15C-Apm.

Conclusions

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References


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