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A concise, stereoselective synthesis of *meso*-2,6-diaminopimelic acid (DAP)

Philip N. Collier,[a] Ian Patel[b] and Richard J. K. Taylor[a,*]

[a]*Department of Chemistry, University of York, Heslington, York YO10 5DD, UK*
[b]*AstraZeneca, Avlon Works, Severn Road, Hallen, Bristol BS10 7ZE, UK*

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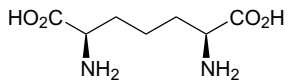
Abstract—The preparation of *meso*-2,6-diaminopimelic acid **1** is described. The key step in the synthesis is Suzuki coupling of the novel organoboron homoalanine equivalent **3** with methyl (2*Z*)-3-bromo-2-[(*tert*-butoxycarbonyl)amino]-2-propenoate **5**.

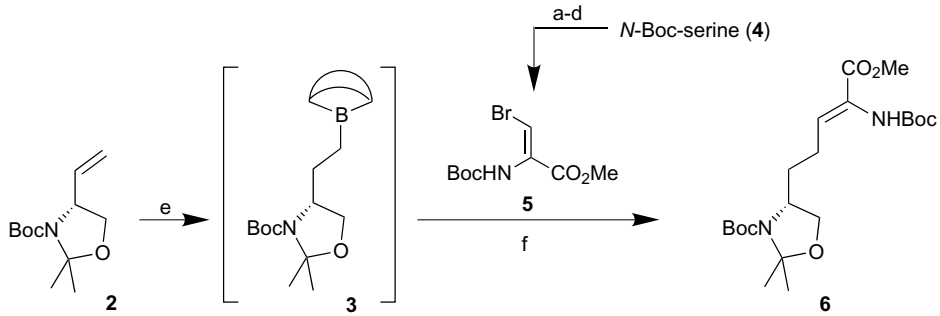
The development of efficient synthetic routes to diaminopimelic acid (DAP) stereoisomers and their analogues has been the focus of considerable recent attention.[1] *meso*-DAP **1**, which is the direct biosynthetic precursor of lysine via the action of *meso*-DAP decarboxylase, is essential for the growth of bacteria and higher plants.[2] In addition, *meso*-DAP confers structural rigidity to many bacteria by cross-linking the polysaccharides of their cell wall peptidoglycan units. The lysine and peptidoglycan functions are not observed in mammalian biochemistry, hence the interest in utilising α,α′-diamino diacids (DADs) as potential antibiotics with low mammalian toxicity.[3] The biological properties of DAP-containing peptides have also been reported and these include antiviral and antitumour activity.[4]



meso-DAP **1**

This letter describes a new synthesis of *meso*-DAP utilising our recently developed organoborane homoalanine anion equivalent **3**,[5] which is readily prepared from the Garner aldehyde-derived alkene **2** (Scheme 1).[6] We envisaged Suzuki coupling[7] between organoborane **3** and a suitably functionalised alkenyl halide to provide the DAP skeleton; asymmetric hydrogenation and oxazolidine hydrolysis–oxidation would then reveal the natural product in protected form. The realisation of this approach is illustrated herein.

The key bromoenamide **5** required for Suzuki coupling with **3** was prepared in four straightforward steps from *N*-Boc-serine in 72% overall yield (Scheme 1).[8,9] The *Z*-configuration of **5** was assigned on the basis of the $^3J_{CH}$ coupling constant of 3.1 Hz between the ester carbonyl carbon and the vinylic proton (after selective decoupling of the ester methyl group and NH exchange



Scheme 1. *Reagents and conditions*: (a) MeI, K_2CO_3, DMF; (b) MsCl, Et_3N, DCM; (c) NBS, DCM; (d) Et_3N, DCM (72% over four steps from **4**); (e) 9-BBN, THF; (f) $PdCl_2(dppf)\cdot CHCl_3$, 3 M K_3PO_4, THF–DMF (76% from **2**).

* Corresponding author. E-mail: rjkt1@york.ac.uk

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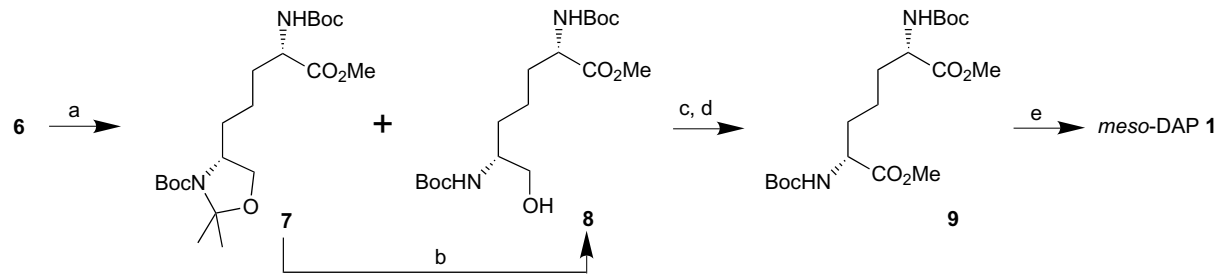

Scheme 2. *Reagents and conditions*: (a) 250 psi H_2, [(COD)Rh((*S*,*S*)-Et-DuPHOS)]OTf, toluene, 60°C (**7**, 79%; **8**, 15%); (b) TFA, MeOH, 0°C, 89%; (c) Jones' reagent, acetone; (d) $TMSCHN_2$, MeOH–toluene (72% from **8**); (e) (i) 5 M HCl, 70°C; (ii) propylene oxide, EtOH (96% from **9**).

with D_2O).[8] We then carried out the Suzuki coupling procedure between organoborane **3** and bromoenamide **5**, using [1,1′ - bis - (diphenylphosphino)ferrocene]dichloropalladium(II) $[PdCl_2(dppf)\cdot CHCl_3]$[7] as catalyst which proved successful in our earlier studies.[5] We were delighted to obtain the desired dehydroamino acid derivative **6** from this reaction in 76% yield $\{[\alpha]_D$ −4.6 (*c* 2.3, $CHCl_3$)}. We have previously shown that alkene stereochemistry is conserved in these types of Suzuki coupling reactions with *Z*-vinylbromides.[5]

Asymmetric hydrogenation of **6** was achieved using Burk's Rh(I)-(*S*,*S*)-Et-DuPHOS catalyst[10] and gave the desired *S*-amino acid product **7** in 79% yield as a single diastereomer[11] (Scheme 2). Alcohol **8** (15%) was also obtained from this reaction. Oxazolidine **7** was converted into **8** using trifluoroacetic acid at 0°C. Oxidation of alcohol **8** was performed using Jones' reagent and the resulting acid was converted into *meso*-diester **9** using TMS–diazomethane. The symmetrical nature of compound **9** was established by proton NMR spectroscopy thus confirming the expected stereoselectivity of the (*S*,*S*)-ligand in the hydrogenation step.[10] Hydrolysis of **9** with 5 M HCl at 70°C followed by treatment with propylene oxide furnished *meso*-DAP **1**, which displayed spectroscopic properties consistent with those published [$\delta_{C=O}$ 173.0 ppm, lit.[12] $\delta_{C=O}$ 172.2 ppm; mp >300°C (dec.); lit.[12] mp >300°C (dec.)].

In principle the above method can be used for the preparation of (*R*,*R*)- and (*S*,*S*)-DAP simply by varying the choice of starting amino acid (L- or D-serine) used in the formation of alkene **2**, and the choice of rhodium catalyst [(*R*,*R*)- or (*S*,*S*)-Et-DuPHOS ligands). This methodology also allows for the preparation of differentially protected DAP analogues for incorporation into peptides. We are currently using this procedure to prepare (*R*,*R*)- and (*S*,*S*)-DAP and novel DAP analogues of biological interest.

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9. All novel compounds were fully characterised by NMR spectroscopy and HRMS.
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11. Hydrogenation of **6** was also carried out under standard H_2–Pd/C conditions to produce a mixture of **7** and the corresponding *R*-amino acid derivative (99%, 52:48). In the asymmetric reaction, the *R*-diastereomer could not be observed by 270 MHz ^1H NMR spectroscopy.
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