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Conjugate addition of radicals generated from diacyloxyiodobenzenes to dehydroamino acid derivatives; a synthesis of diaminopimelic acid analogues

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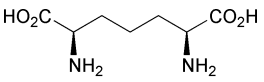
Radical decomposition of bis((2*S*)-*N*-benzyloxycarbonyl-2-aminopentan-5-carboxy-1-methyl ester)iodobenzene followed by decarboxylation and subsequent conjugate addition with a series of selectively protected dehydroamino acids leads to new analogues of diaminopimelic acid.

Inhibition of the biosynthesis of the cell wall layer in bacteria has become a major strategy in the development of new antibiotics.[1] In particular the inhibition of the biosynthetic pathway leading to *meso*-diaminopimelic acid (DAP) **1**, a key



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constituent of the peptidoglycan cell wall layer in Gram negative bacteria has attracted much attention.[2] Several studies have shown that inhibitors of the DAP pathway possess antibiotic activity and this has led to many syntheses of **1** and its analogues.[2–4] Although elegant approaches to **1** have been reported, the major synthetic problem generally consists of facile stereocontrolled assembly of derivatives with orthogonal protection on the two amino and the carboxy functions. This permits manipulation of each of the four functionalities for preparation of DAP containing peptides which have been shown to exhibit diverse biological activities.[2,4,5] We now report an investigation into the synthesis of selectively protected DAP derivatives using the conjugate addition of protected amino acid radicals generated from diacyloxyiodobenzenes with a series of dehydroamino acid derivatives.

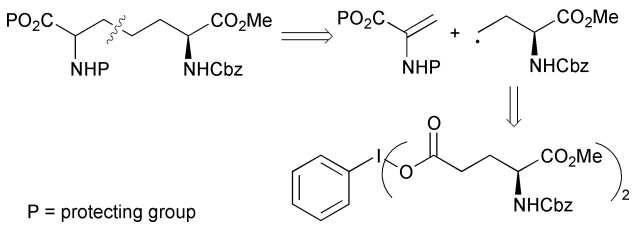
The conjugate addition of radicals with dehydroamino acid derivatives has been reported by the groups of both Beckwith and Jones who use either mercury or tin compounds during the reaction process.[6–8] We were interested in using an approach with less toxic reagents, such as the generation of an amino acid radical by decomposition and decarboxylation of a diacyloxyiodobenzene (Scheme 1). It seemed that capture of this radical with a protected dehydroamino acid and reduction with a hydrogen donor should give the DAP skeleton.

Two diacyloxyiodobenzenes were prepared in good yield using a procedure involving reaction of two equivalents of a commercially available glutamate with (diacetoxyiodo)benzene **2** in the presence of a high boiling solvent (Scheme 2).[9] This reaction is reversible. However, the equilibrium can be shifted towards the synthesis of the glutamate-derived diacyloxyiodobenzene by distillation under reduced pressure of the relatively volatile acetic acid formed during the reaction.

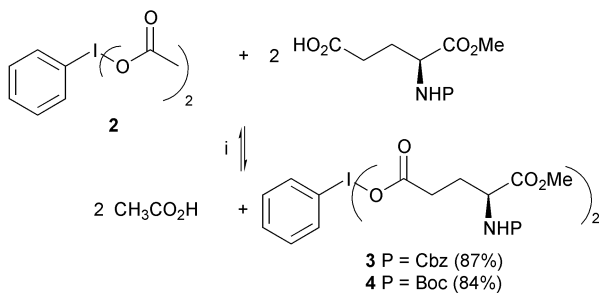
Two achiral dehydroamino acid substrates, **5** and **6** were then prepared by base elimination of an analogous mesylate derived from a suitably protected serine analogue (Table 1).[10] For the stereoselective synthesis of the DAP skeleton, it seemed plausible that a dehydroamino acid analogue containing one or more stereogenic centres would, after conjugate attack, exert facial control over hydrogen atom transfer from the hydrogen donor.[6,7] Therefore, dehydroamino acid analogues, **7** and **8** were generated from a Williams oxazinone and a Seebach oxazolidinone, respectively, using reported procedures.[7,11] Finally, dehydroamino acid analogue, **9** (entry 3) was made by alkylation of (2*R*)-1-benzoyl-2-(1,1-dimethylethyl)-3-methyl-4-imidazolidinone with chloromethyl benzyl ether followed by elimination of benzyl alcohol with LDA (61% for the two steps).

A series of reactions was then done using the diacyloxyiodobenzene **3** with these dehydroamino acid derivatives under themolysis conditions with benzene as the solvent and 1,4-cyclohexadiene as the hydrogen donor (Table 1).[12] Extended reaction times of up to 12 hours were required for complete consumption of the relatively stable trivalent iodobenzene **3**. Reaction of **3** with dehydroamino acids **5**, **6**, **7** and **9** (entries 1–4) gave in each case the unsaturated adduct in modest yields. In certain cases, such compounds are formed by disproportionation of the radical intermediate after conjugate addition to give a saturated and unsaturated version of the analogue.[12] However, in these examples none of the saturated compound could be detected. The unsaturated adducts may be formed by abstraction of a hydrogen atom from the carbon adjacent to the radical centre (generated through conjugate addition) by the iodine radical intermediate to give iodobenzene and *N*-Cbz-L-glutamic acid α-methyl ester as the other products. An alternative possibility is electron transfer from the initial adduct followed by proton loss (*i.e.* elimination). This suggests that the radical formed after conjugate addition is sterically crowded and cannot readily abstract a hydrogen atom from 1,4-cyclohexadiene.

Surprisingly, reaction of diacyloxyiodobenzene **3** with dehydroamino acid analogue **8** gives the dimerisation product in 35% yield as a single diastereomer (entry 5). A similar result was obtained using the Boc-protected glutamate derived iodobenzene **4** (entry 6). Efforts to prove the absolute



Scheme 1



Scheme 2 *Reagents and conditions*: i, chlorobenzene, 50 °C.

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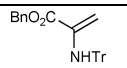
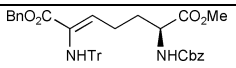
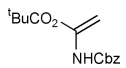
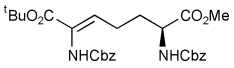
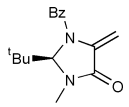
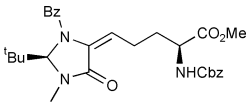
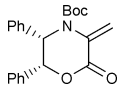
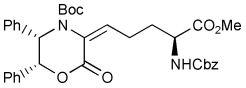
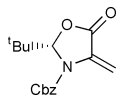
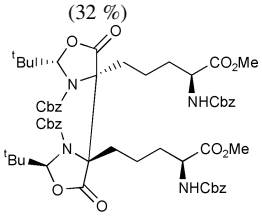
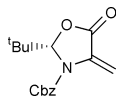
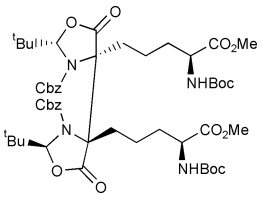
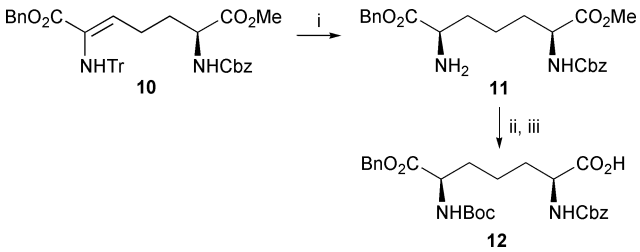
Table 1 Conjugate addition of radicals derived from diacyloxyiodobenzenes with dehydroamino acids

Entry[a]	Dehydro-amino acid	Diacyloxy-iodobenzene	Product (yield)
1	 **5**	**3**	 **10** (44 %)
2	 **6**	**3**	 (54 %)
3	 **9**	**3**	 (44 %)
4	 **7**	**3**	 (32 %)
5	 **8**	**3**	 (35 %)
6	 **8**	**4**	 (35 %)

[a] All reactions were carried out using 1,4-cyclohexadiene (5.0 equiv.) in benzene under reflux for 12 h.

stereochemistry of these dimerisation products either by NMR spectroscopy or X-ray crystallography were unsuccessful. However, it is likely that after conjugate addition, dimerisation takes place from the least hindered face of the oxazolidinone ring to give the dimerisation products with absolute stereochemistry as shown in Table 1. These intriguing results suggest that the conjugate adduct radical while not accessible enough to abstract a hydrogen atom from 1,4-cyclohexadiene can still undergo dimerisation. It should be noted that none of the unsaturated adducts were isolated from either of these two reactions. Entry 5 was also repeated under photolytic conditions using a high pressure mercury lamp as the source of irradiation. However, as with the thermolysis conditions, only the dimerisation product was isolated (25% yield). In a further series of experiments other sources of hydrogen donors were studied. Entry 5 was repeated using tributyltin hydride, trimethyl orthoformate or triethylsilane under thermolysis conditions.[12] These reactions gave very complex mixtures of products, with neither the dimers nor the unsaturated derivatives being produced in isolable amounts.

Due to the inability of this approach to directly produce the saturated skeleton of DAP, we examined reduction of an unsaturated derivative to give the desired selectively-protected skeleton. Stereoselective hydrogenation of unsaturated protected DAP skeletons to make DAP isomers is well precedented.[4,13] Therefore, the unsaturated derivative **10** was hydrogenated with [(COD)Rh((*R*,*R*)-Et-DuPHOS)]BF_4 using the conditions described by Burk and co-workers (Scheme 3).[14]



Scheme 3 *Reagents and conditions*: i, [(COD)Rh((*R*,*R*)-Et-DuPHOS)]BF_4, MeOH, 100 psi, H_2, 59%; ii, Boc_2O, NEt_3, DMAP, CH_2Cl_2, 95%; iii, LiOH, MeOH, H_2O, 59%.

This procedure, as well as removing the trityl protecting group, gives the *meso*-DAP derivative **11** in a 9:1 mixture of diastereomers (by ^1H NMR spectroscopy). This fortuitous result obviously allows selective manipulation at this stage of one of the amino groups. To show orthogonality of the carboxy functions, the amino group was re-protected with Boc_2O and then treated with one equivalent of lithium hydroxide. This led to the hydrolysis of predominantly the methyl ester to give the mono-acid **12** in 59% yield.

In summary, thermolysis of glutamate-derived iodobenzenes leads to primary radicals which can be captured by dehydroamino acids by conjugate addition. In contrast to related systems,[12] the newly formed secondary radical, is not reduced by 1,4-cyclohexadiene or other hydrogen atom donors, resulting in production of unsaturated adducts and dimerisation products. Chiral hydrogenation of an unsaturated derivative gives selectively-protected DAP. Orthogonality of protection has also been demonstrated.

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