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Synthesis of Protected 3-Methylaspartic Acids from Glutamic Anhydride *via* Nickelacycles

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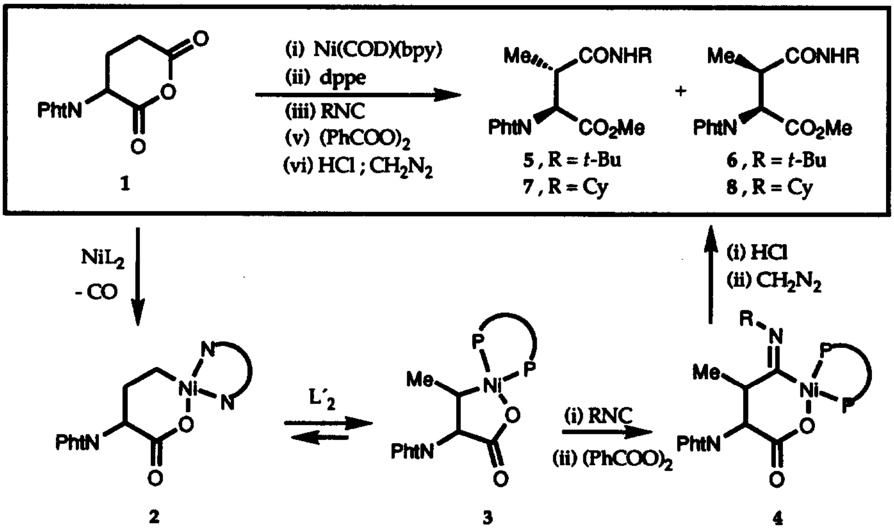
Abstract: The synthesis of fully protected β-methyl aspartic acids from (±)-glutamic anhydride has been achieved by means of ring contraction of the derived nickelacycle followed by insertion of an isocyanide. The intermediate five-membered ring nickelacycles were isolated and characterized spectroscopically.

The synthesis of β-methylaspartic acids is of interest since the *erythro* isomer is a constituent of certain cyclic peptides such as nodularine, motuporine, and the microcystines (cyanoginosines)[1]. Recently developed syntheses of this amino acid are based on the stereoselective alkylation of protected derivatives of aspartic acid.[2,3] On the other hand, the bacterium *Clostridium tetanomorphum* synthesizes*threo*-(2*S*,3*S*)-3-methylaspartic acid from (2*S*)-glutamic acid in a single step by means of a fascinating intramolecular rearrangement catalyzed by the cobalamin enzyme glutamate mutase.[4,5] Herein we report a conceptually new synthesis of protected derivatives of (±)-β-methylaspartic acid from the anhydride of (±)-*N*-phthaloylglutamic acid (**1**) based on nickelacycles following the reaction pathway outlined in the Scheme.[6]



We have recently shown that the oxidative addition of *N*-phthaloylglutamic anhydride (**1**) to Ni(COD)bpy proceeds regioselectively through the C-5 carbonyl group leading, after decarbonylation, to a six-membered nickelacycle (**2**) (Scheme).[7] This nickelacycle can equilibrate with the five-membered ring complexes (**3**) by a β-hydride elimination-insertion process. We expected that addition of the chelating diphosphine 1,2-bis(diphenylphosphino)ethane (dppe) would shift this equilibrium to give a mixture of *cis* and *trans* five-membered ring nickelacycles.[8] Furthermore, reaction of these nickelacycles with an isocyanide would lead to the insertion derivatives (**4**). Hydrolysis of these intermediates would furnish the desired 3-methylaspartic acids (Scheme). Employment of an isocyanide, as a surrogate of carbon monoxide, should allow for the differentiation of the carboxyl functions.

The above transformations were initiated by treatment of (±)-**1** with Ni(COD)(bpy) (1.5 equiv)[8] in THF at 50 °C for 6.5 h, followed by addition of a solution of dppe (1.5 equiv) in CH_2Cl_2 for 16 h. Reaction of the intermediate nickelacycles with *t*-butylisocyanide (3 equiv) for 3.5 h followed by addition of dibenzoylperoxide (1.6 equiv) in THF gave the desired β-methylaspartic acid derivatives after mild acid hydrolysis. This transformation was performed in a single operation, without isolation of intermediates. Treatment with diazomethane afforded a 3:1 mixture of *threo* and *erythro* derivatives **5** and **6**[9] in 55 % overall yield from **1**. Addition of dibenzoylperoxide was found to be necessary in order to obtain the insertion derivatives.[10] Similar results were obtained with cyclohexylisocyanide (2.7:1 mixture of **7** and **8**).[9] Interestingly, addition of only 1.5 equiv of *t*-BuNC gave a 1:1.3 ratio of isomers, favouring the *erythro* derivative.

The relatively stable yellow five-membered ring nickelacyles **3**[11] could be isolated as a 1.3:1 mixture of *trans* and *cis* isomers after addition of dppe. Carbonylation of **3** with 1 atm of CO at 25 °C proceeded smoothly to yield a 2:1 mixture of trans and cis 3-methylaspartic acid anhydrides. On the other hand, reaction with *t*-butylisocyanide led to a 2:1 mixture mixture of *threo* and *erythro* derivatives, after acid hydrolysis.

In summary, we have demonstrated that a synthesis of β-methylaspartic acids from glutamic anhydride is possible by means of organonickel chemistry. Studies are now in progress to search for other bidentate ligands with improved stereochemical performances.

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6. Abbreviations: COD = 1,5-cyclooctadiene; bipy = 2,2'-bipyridine; Cy = cyclohehexyl; dppe = 1,2-bis(diphenylphosphino)ethane.
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9. These products were characterized spectroscopically and their stereochemistries were determined by comparison with products derived from commercially available *rac-threo*-3-methylaspartic acid.
10. Addition of this oxidant also promotes the insertion of CO in related nickelacylces.
11. The nickelacycles were characterized by ^{1}H, $^{1}H\{^{31}P\}$, $^{31}P\{^{1}H\}$, and $^{13}C\{^{1}H\}$ NMR in $CDCl_3$ and IR.

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