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Synthesis of 3-Methylaspartic Acids by Ring-Contraction of a Nickelacycle Derived from Glutamic Anhydride

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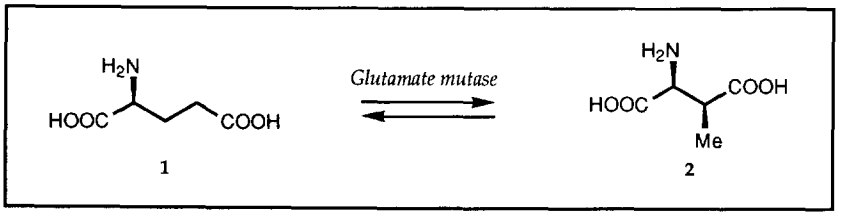
Abstract: The synthesis of protected methylaspartic acids from glutamic acid has been achieved by means of ring contraction of the derived nickelacycle followed by insertion of isocyanides.

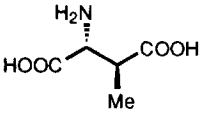
Introduction

The conversion of (2*S*)-glutamic acid (**1**) into *threo*-(2*S*,3*S*)-3-methylaspartic acid (**2**) is a fascinating intramolecular rearrangement catalyzed by the cobalamin enzyme glutamate mutase of the bacterium *Clostridium tetanomorphum*.[1,2] This most economical production of **2** involves a migration of the glycine portion (C-1/C-2) to C-4.[3]



1 **2**

The synthesis of β-methylaspartic acids[4,5] is of interest since the *erythro* isomer **3**, (2*R*,3*S*)-3-methylaspartic acid, is a constituent of certain cyclic peptides[6] such as nodularine,[7] motuporine,[8] and the microcystines (cyanoginosines).[9,10] Recently developed syntheses of **3** are based on the stereoselective alkylation of protected derivatives of aspartic acid.[7,11,12]

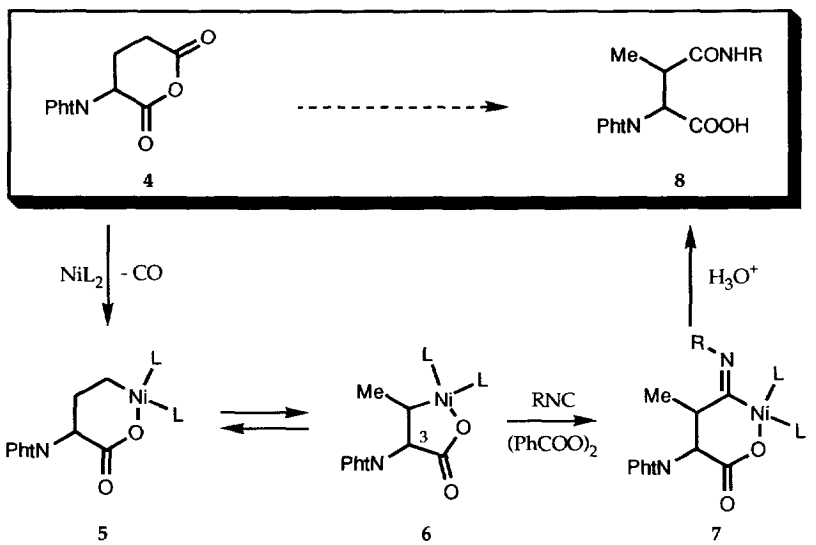


3

We became intrigued by the prospect of synthesizing 3-methylaspartic acids from a suitable derivative of **1** by using nickelacycles as intermediates. We have recently shown that the oxidative addition of *N*-phthaloylglutamic anhydride (**4**) to Ni(COD)bpy[13] proceeds regioselectively through the C-5 carbonyl group leading, after decarbonylation, to a six-membered nickelacycle (**5**) (Scheme 1).[14] In principle, this nickelacycle could equilibrate with the five-membered ring complexes (**6**)[15] by a β-hydride elimination-

insertion process. Based on the precedent reported by Yamamoto,[16] we expected that addition of the chelating diphosphine dppe would shift this equilibrium to give a mixture of *cis* and *trans* five-membered ring nickelacycles. Presumably, the stereochemical outcome of this process could be governed by the steric bulk of the ligands on Ni and the amine protective group. Furthermore, reaction of these nickelacycles with an isocyanide would lead to the insertion derivative **7**. Hydrolysis of this intermediate would furnish the desired 3-methylaspartic acid derivatives **8** (Scheme 1). Employment of an isocyanide, as a surrogate of carbon monoxide, should allow for the differentiation of the carboxyl functions.[15] In this paper we report full details on the synthesis of protected derivatives of β-methylaspartic acid from (±)-*N*-phthaloylglutamic anhydride (**4**) following the reaction pathway outlined in Scheme 1.[17]

Scheme 1

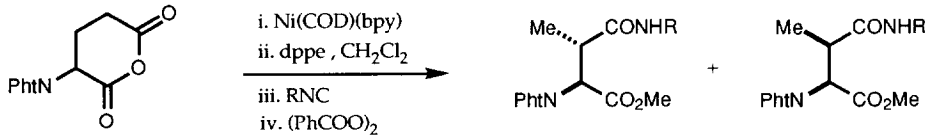


Results and Discussion

Treatment of anhydride **4** with Ni(COD)(bpy) (1.5 equiv), prepared *in situ* by treating $Ni(COD)_2$ with 1 equiv of bpy, 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 furnished the ring contracted nickelacycles **6** as a mixture of *cis* and *trans* isomers. Reaction of the intermediate nickelacycles with *tert*-butyl isocyanide (3 equiv) for 3.5 h followed by addition of benzoylperoxide (1.5 equiv) in THF gave the desired 3-methylaspartic acid derivatives after mild acid hydrolysis. This transformation was performed in a single operation without isolation of intermediates. The mixture of acids was esterified with diazomethane to yield a 3:1 mixture of *threo* and *erythro* derivatives **9** and **10** in 55 % overall yield from **4** (Eq 1). A similar ratio of amides **11** and **12** was obtained with cyclohexyl isocyanide. Addition of only 1.5 equiv of *tert*-BuNC gave a 1:1.3 ratio of isomers, favoring the *erythro* derivative (Eq 1).

Addition of benzoylperoxide was found to be necessary in order to obtain the insertion derivatives. The role of the peroxide in this transformation is unclear, although it has been found that the addition of this oxidant also promotes the insertion of CO into the Ni-C bond.[15]

Eq 1



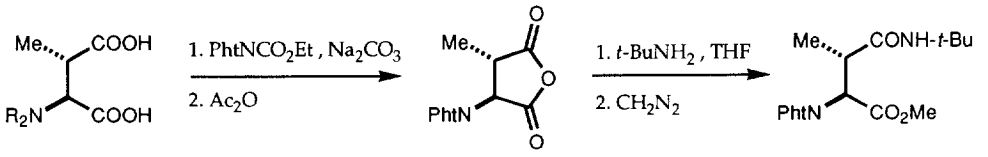
4

9 , R = *t*-Bu
11 , R = Cy

10 , R = *t*-Bu
12 , R = Cy

The stereochemical assignments were secured by comparison with **9** obtained regioselectively from (±)-*N*-phthaloyl *threo*-3-methylaspartic anhydride (**13**) as shown in Scheme 2. Anhydride **13** was prepared in quantitative yield from commercially available *threo*-3-methylaspartic acid (**14**) by N-protection with *N*-ethoxycarbonyl phthalimide and aqueous Na_2CO_3 to give **15**,[18] followed by dehydration with Ac_2O under reflux. The reaction of **13** with *tert*-butylamine proceeded regioselectively leading to a single amide, which was methylated with excess diazomethane to give **9**. The alternative opening of the anhydride with methanol proceeded with low regioselectivity to give a 1:1.4 ratio of the corresponding α and β-methyl esters.

Scheme 2



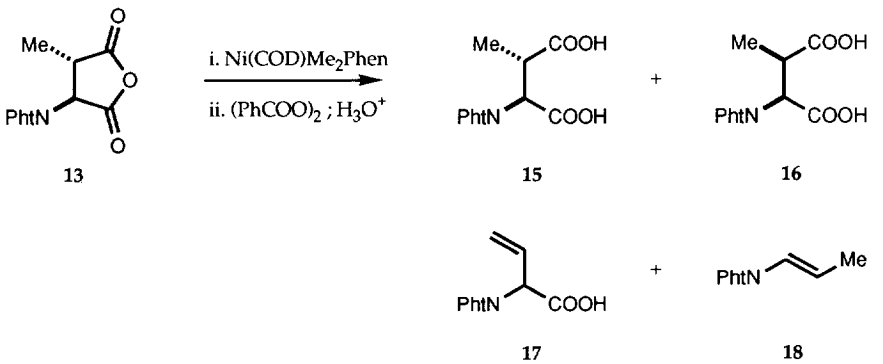
14 , R = H
15 , R_2 = Pht

13

9

Reaction of anhydride (±)-**13** with Ni(COD)Me_2Phen in THF at 23 °C,[15] followed by addition of benzoylperoxide and acid hydrolysis led to a 2.7:1 mixture of *threo*- and *erythro*-3-methylaspartic acid derivatives **15** and **16**. Additionally, vinylglycine derivative **17** and (*E*)-*N*-(1-propenyl)phthalimide **18** were also detected in the crude reaction mixture as byproducts (Eq 2).

Eq 2



13

15

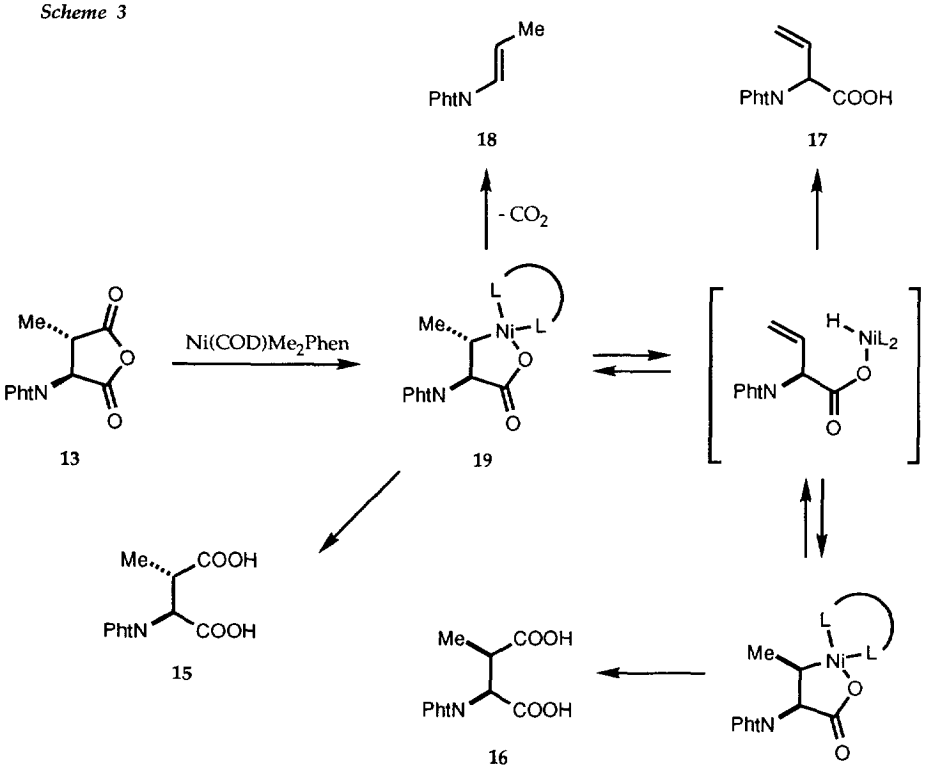
16

17

18

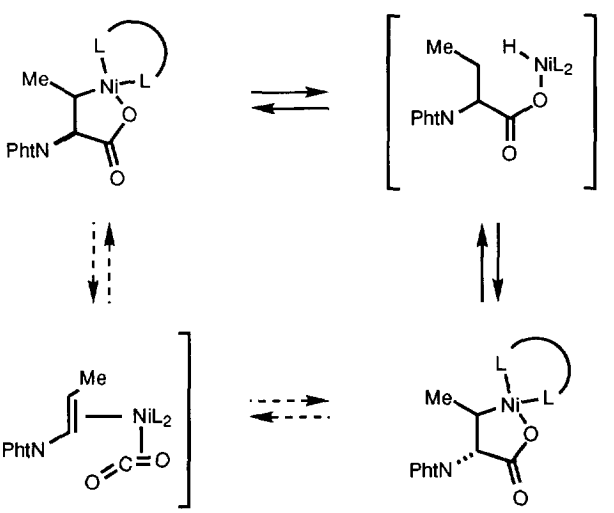
The formation of stereoisomer **16** from anhydride **13** demonstrates that the primary five-membered ring nickelacycle **19** suffers a rapid β-hydride elimination-reinsertion reaction leading to an equilibrium mixture of diastereomers (Scheme 3). While this reaction scheme also accounts for the formation of **17**, the isolation of alkenylphthalimide **18** indicated that nickelacycle **19** decomposes by an alternative pathway. Cycloreversion of **19** would lead to alkene **18** and CO_2. Alkene **18** could also derive from the minor regioisomer of **19** resulting by reaction of the nickel(0) complex through the C-1 carboxyl of **13**.[14] The reverse reaction, nickel(0)-mediated oxidative coupling of CO_2 with alkenes or alkynes to give nickelacycles has been reported.[19]

Scheme 3



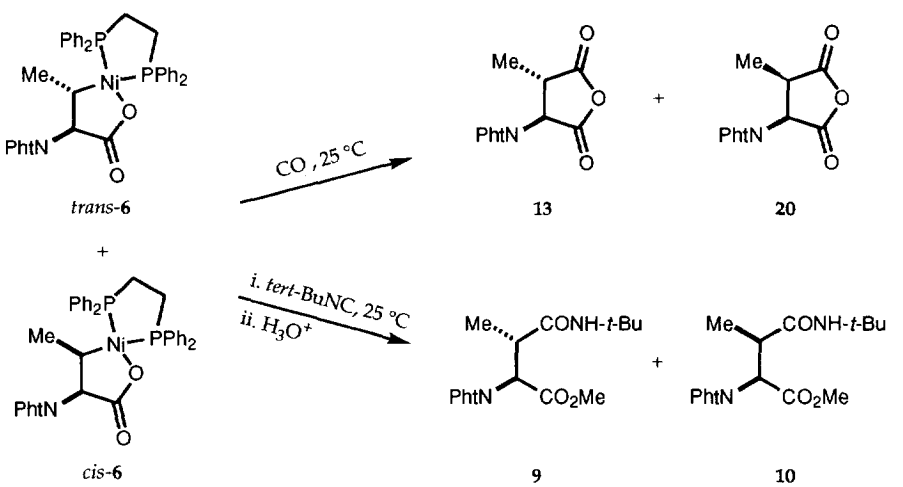
Unfortunately, when the procedure shown in Eq 1 was performed starting from optically pure *N*-phthaloyl-L-glutamic anhydride and *tert*-butyl- or cyclohexyl isocyanide, racemic mixtures of *threo* and *erythro* derivatives were obtained, as shown by ^1H NMR analyses of the methyl esters derivatives in the presence of the chiral shift reagent europium(III) tris[3-(heptafluoropropylhydroxymethylene)]-(+)-camphorato. This result indicates that the intermediate five-membered nickelacycles formed by decarbonylation and ring-contraction undergo facile β-hydride elimination-insertion leading to the loss of stereochemical integrity at C-3 (nickelacycle numbering) (Scheme 4).[15] The racemization could also be explained by an alternative mechanism proceeding by reversible cycloreversion of the nickelacycles to form an achiral η^2-alkene complex of nickel(0) as an intermediate.[19] The loss of optical activity could also occur at the stage of the starting anhydride or the intermediate nickelacycles by a base-catalyzed process.[15]

Scheme 4



The intermediate five-membered ring nickelacycles **6** formed from **4** and Ni(COD)bpy were isolated as a yellow solid after addition of dppe (Scheme 1). ^{1}H and ^{31}P NMR showed a 1.3:1 mixture of *trans* and *cis* isomers whose ratio remained constant at this equilibrium value after 48 h at 25 °C in $CDCL_3$. The complex $Ni(CO)_2dppe$[20] was also isolated from the orange filtrate in the reaction of **4** with Ni(COD)dppe. This complex results from reaction of the excess Ni(0) reagent with the CO eliminated in the first steps of the process, followed by ligand exchange with dppe. The diastereomeric nickelacycles are stable in the solid state under an inert atmosphere or in $CDCl_3$ solution for several hours at 25 °C. Their NMR data are analogous to those of a related nickelacycle derived from aspartic acid.[15] However, because of overlapping of the H-3 signal with the multiplets due to chelating diphosphinethe, the relative stereochemistry of each metallacycle could not be determined unambiguously, although it was assumed that the major product was *trans*-**6** on the basis of the stereochemistry of the major products obtained by treatment with CO and isocyanides (Scheme 5).

Scheme 5



Carbonylation of nickelacycles **6** with 1 atm of CO at 25 °C for 24 h afforded a 2:1 mixture of *trans*- and *cis* 3-methylaspartic acid anhydrides **13** and **20** (Scheme 5). The carbonylation reaction was shown to be reversible under these conditions. Starting with a 1:1 mixture of diastereomeric nickelacycles **6**, carbonylation led almost immediately to a 1:1 mixture of **13** and **20**. However, on standing under CO for 7 days a 2.3:1 ratio of anhydrides **13** and **20** was obtained. On the other hand, reaction of **6** with *tert*-butyl isocyanide proceeded smoothly at 25 °C leading, after acid hydrolysis, to a 2:1 mixture of *threo* and *erythro* derivatives **9** and **10**.

Conclusions

We have shown that a synthesis of 3-methylaspartic acids derivatives is possible starting from glutamic anhydride by oxidative addition to a nickel(0) complex followed by ring contraction and isocyanide insertion. This process leads to the formation of the *threo* diastereomer as the major product. A similar stereochemical result was obtained starting from the anhydride of *threo*-3-methylaspartic acid. The intermediate five-membered ring nickelacycles were isolated as a mixture of *trans* and *cis* isomers and were characterized spectroscopically and by their reactions with CO and *tert*-butyl isocyanide. Unfortunately, the nickelacycles probably suffer facile β-hydride elimination under the reaction conditions leading to the formation of racemic products from an optically active starting material. Further work directed to the development of new nickelacycles is in progress.

Experimental Section

General procedures. All reactions were carried out under Ar. Solvents were dried by standard methods. Chromatographic purifications were carried out with columns packed with flash grade silica gel. Cyclooctadiene (COD) was distilled over CaH_2. $Ni(COD)_2$ was prepared by reduction of $Ni(py)_4Cl_2$ with Na in the presence of COD according to a known procedure.[21]

(±)-*N*-phthaloylglutamic anhydride (4).[22]

A suspension of glutamic acid (2.94 g, 20.0 mmol) and phthalic anhydride (3.02 g, 20.0 mmol) in pyridine (35 mL) was heated under reflux conditions for 1.5. The solvent was evaporated and the residue was heated in acetic anhydride (20 mL) under reflux conditions for 5 min. The mixture was evaporated (Kugelrohr, 0.1 mm Hg, 75 °C) to give crude **4**. Recrystallization from 1,4-dioxane yielded **4** as a white solid (3.85 g, 74%): mp 178-179 °C, lit.[22] 189-190°C.

Optically active **4** was prepared from known *N*-phthaloyl-L-glutamic acid,[23] mp 157-159°C, lit[22] 160 °C; $[\alpha]_D$ -49.1 ± 0.4° (c 1, 1,4-dioxane), lit[23] $[\alpha]_D$ -48.3° (c 3, 1,4-dioxane), by the following procedure: A suspension of *N*-phthaloyl-L-glutamic acid (500 mg, 1.80 mmol) in acetic anhydride (2 mL) was heated at 100 °C until a clear solution was obtained. The solution was cooled at -15 °C for 24 h and the solid was filtered to give L-**4** as a white solid (335 mg, 74%): mp 200-202 °C, lit.[24] 199-201 °C; $[\alpha]_D$ -47.0° (c 1, 1,4-dioxane), lit.[24] $[\alpha]_D$ -38.0° (c 3, 1,4-dioxane).

***(RS,RS)*-*N*-*tert*-butyl-N^2-phthaloyl-3-methylasparagine methyl ester (9) and *(RS,SR)*-*N*-*tert*-butyl-N^2-phthaloyl-3-methylasparagine methyl ester (10).**

A solution of anhydride **4** (181 mg, 0.7 mmol) and bpy (156 mg, 1 mmol) in THF (10 mL) was added to $Ni(COD)_2$ (275 mg, 1 mmol) and the resulting mixture was stirred at 50 °C for 6.5 h. A solution of dppe

(398 mg, 1 mmol) in CH_2Cl_2 (10 mL) was added and the mixture was stirred at 23 °C for 16 h. The resulting yellow suspension was treated with *tert*-butyl isocyanide (0.23 mL, 2 mmol). After being stirred for 3.5 h at 23 °C a solution of benzoylperoxide (266 mg, 1.1 mmol) in THF (2 mL) was added. After being stirred for 5 h, the mixture was hydrolyzed with con 1.2 M aqueous HCl and extracted with EtOAc. The organic solution was extracted with 5% aqueous $NaHCO_3$, and the aqueous extract was acidified with 1.2 M aqueous HCl, and extracted with EtOAc. The organic extract was dried (Na_2SO_4) and evaporated to give a mixture of 3-methylasparagine derivatives and benzoic acid. Methylation with excess CH_2N_2 in Et_2O followed by chromatography (3:1 hexane-EtOAc) led to a 3:1 mixture of **9** and **10** (133 mg, 55 %).

IR (KBr) 3310, 1780, 1740, 1725, 1650, 1390, 1265, 720 cm^{-1}; MS *m/z* 346 (M^+, 5), 274 (45), 246 (85), 214 (100), 188 (46), 130 (32). **9**: ^1H NMR (200 MHz, $CDCl_3$) δ 7.87-7.81 (m, 2H), 7.77-7.69 (m, 2H), 5.55 (s, 1H), 5.33 (d, J = 10.6 Hz, 1H), 3.65 (s, 3H), 3.11 (dq, J = 10.6, 7.1 Hz, 1H), 1.37 (s, 9H), 1.02 (d, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$) δ 173.02, 169.19, 167.48, 134.28, 131.65, 123.64, 53.27, 52.60, 51.23, 28.67, 15.84. **10**: ^1H NMR (200 MHz, $CDCl_3$) δ7.87-7.81 (m, 2H), 7.77-7.69 (m, 2H), 5.47 (s, 1H), 4.91 (d, J = 9.6 Hz, 1H), 3.70 (s, 3H), 3.34 (dq, J = 9.6, 6.7 Hz, 1H), 1.38 (d, J = 6.7 Hz, 3H), 1.05 (s, 9H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$) δ 171.28, 169.06, 167.29, 134.22, 131.72, 123.64, 54.49, 52.67, 50.87, 41.81, 28.27, 16.35.

(*RS*,*RS*)-*N*-cyclohexyl-N^2-phthaloyl-3-methylasparagine methyl ester (11) and (*RS*,*SR*)-*N*-cyclohexyl-N^2-phthaloyl-3-methylasparine methyl ester (12).

These compounds were prepared from **4** as above using cyclohexyl isocyanide followed by methylation with excess CH_2N_2. Chromatography (3:1 hexane-EtOAc) led to a 2.7:1 mixture of **11** and **12** (19% overall yield).

IR (KBr) 3320, 2930, 2850, 1780, 1745, 1720, 1640, 1395, 720 cm^{-1}; MS *m/z* 373 (M^+ + 1, 5), 372 (M^+, 7), 341 (7), 274 (19), 246 (70), 214 (100). **11**: ^1H NMR (200 MHz, $CDCl_3$) δ 7.89-7.86 (m, 2H), 7.76-7.73 (m, 2H), 5.53 (d, J = 8.3 Hz, 1H), 5.36 (d, J = 10.6 Hz, 1H), 3.66 (s, 3H), 3.17 (dq, J = 10.5, 7.1 Hz, 1H), 2.05-1.05 (m, 11H), 1.05 (d, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$) δ 172.79, 169.14, 167.49, 134.34, 131.58, 123.70, 53.26, 48.23, 40.74, 32.99, 25.53, 24.84, 24.78, 15.87. **12**: ^1H NMR (200 MHz, $CDCl_3$) δ 7.89-7.86 (m, 2H), 7.76-7.73 (m, 2H), 5.56 (d, overlapping with the NH signal of **11**, 1H), 4.97 (d, J = 8.9 Hz, 1H), 3.72 (s, 3H), 3.41 (dq, J = 8.9, 6.8 Hz, 1H), 2.05-1.05 (m, 11H), 1.38 (d, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$) δ 171.02, 169.14, 167.49, 134.20, 131.58, 123.60, 52.72, 47.70, 41.16, 32.65, 25.34, 24.64, 24.53, 16.21.

Synthesis of 9 from *threo*-3-methylaspartic acid (14) (Scheme 2).

(i) (±)-*threo*-*N*-Phthaloyl-3-methylaspartic acid (**15**): A suspension of **14** (100 mg, 0.68 mmol), Na_2CO_3 (76 mg, 0.72 mmol), and *N*-ethoxycarbonylphthalimide (159 mg, 0.72 mmol) in H_2O (1.50 mL) was stirred at 23 °C for 6.5 h. After being cooled to room temperature, the mixture was washed with EtOAc, acidified with 1.2 M aqueous HCl, and extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4) and evaporated to give **15** as a white solid (198 mg, quantitative): mp 186-189 °C (H_2O), lit.[18] 199-202 °C (dec.).

IR (KBr) 3700-2840, 1785, 1760, 1705, 1400, 730 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.96-7.89 (m, 4H), 4.94 (d, J = 10.8 Hz, 1H), 3.18 (dq, J = 10.9, 7.3 Hz, 1H), 0.96 (d, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (50 MHz, DMSO-d_6) δ 175.20, 169.43, 167.26, 135.05, 130.84, 123.61, 52.77, 38.42, 14.65; MS *m/z* 277 (M^+, 0.2), 259 (3), 187 (100), 169 (29), 104 (35), 76 (43). Anal Calcd for $C_{13}H_{11}NO_6$: C, 56.32; H, 4.00; N, 5.05. Found: C, 56.06; H, 4.30; N, 5.11.

(ii) (±)-*threo*-*N*-Phthaloyl-3-methylaspartic anhydride (**13**): A suspension of acid **15** (50 mg, 0.18 mmol) in Ac_2O (1 mL) was heated under reflux conditions for 5 min. The mixture was evaporated to give **13** as a white solid (46 mg, quantitative).

IR (KBr) 1875, 1790, 1720, 1405, 975, 720 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.97-7.89 (m, 4H), 5.42 (d, J = 8.3 Hz, 1H), 3.65 (dq, J = 8.2, 7.0 Hz, 1H), 1.34 (d, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (50 MHz, DMSO-d_6) δ 171.63, 168.35, 165.54, 135.09, 131.11, 123.73, 53.47, 39.83, 12.43; MS *m/z* 187 (100), 169 (39), 104 (29), 76 (42).

(iii) (*RS,RS*)-*N*-*tert*-Butyl-N^2-phthaloyl-3-methylasparagine methyl ester (**9**): A solution of anhydride **13** (20 mg, 0.08 mmol) and *tert*-butylamine (0.040 mL, 0.38 mmol) in THF (2 mL) was stirred at 23 °C for 36 h. The mixture was treated with 1.2 M aqueous HCl and extracted with EtOAc. The organic extract was dried (Na_2SO_4) and evaporated to give a yellowish semisolid.

^1H NMR (300 MHz, $CDCl_3$) δ 7.89-7.86 (m, 2H), 7.76-7.73 (m, 2H), 5.57 (br s, 1H), 5.35 (d, J = 10.5 Hz, 1H), 3.20 (dq, J = 10.5, 7.1 Hz, 1H), 1.36 (s, 9H), 1.07 (d, J = 7.1 Hz, 3H). The semisolid was dissolved in CH_2Cl_2 (2 mL) and was treated with excess CH_2N_2 in Et_2O. The solution was evaporated to give a white solid. Recrystallization (Et_2O-hexane) gave **9** (25 mg, 95%), identical with the major compound prepared from anhydride **4**. Anal. Calcd for $C_{18}H_{22}N_2O_5$: C, 62.42; H, 6.40; N, 8.09. Found: C, 62.18; H, 6.70; N, 7.95.

Reaction of anhydride 13 with Ni(COD)Me_2Phen.

To a solution of Me_2Phen (45 mg, 0.22 mmol) and $Ni(COD)_2$ (65 mg, 0.24 mmol) in THF (1.5 mL) was added anhydride **13** (35 mg, 0.13 mmol) in THF (1.5 mL). After being stirred at 23 °C for 6 h, benzoylperoxide (64 mg, 0.26 mmol) was added and the mixture was hydrolyzed with 1.2 M aqueous HCl. Extraction with EtOAc gave a 6.6:2.4:2.3:1 mixture of **15**, **16**, **17**, and **18**, which was not separated.

16-dimethyl ester, prepared by treatment of the crude reaction mixture with excess diazomethane: ^1H NMR (200 MHz, $CDCl_3$) δ 7.89-7.86 (m, 2H), 7.76-7.73 (m, 2H), 5.12 (d, J = 7.8 Hz, 1H), 3.74 (s, 3H), 3.63 (s, 3H), 3.50 (m, 1H), 1.40 (d, J = 7.1 Hz, 3H). **17**: ^1H NMR (300 MHz, DMSO-d_6) δ 7.89-7.86 (m, 2H), 7.80-7.70 (m, 2H), 6.28 (ddd, J = 17.0, 10.5, 6.1 Hz, 1H), 5.89 (dt, J = 6.1, 1.6 Hz, 1H), 5.26 (dt, J = 10.6, 1.1 Hz, 1H), 5.23 (dt, J = 17.1, 1.3 Hz, 1H). **18**: ^1H NMR (200 MHz, $CDCl_3$) δ 7.89-7.86 (m, 2H), 7.76-7.73 (m, 2H), 6.84 (dq, J = 15.5, 6.9 Hz, 1H), 5.78 (dq, J = 15.5, 1.7 Hz, 1H), 1.79 (dd, J = 6.9, 1.7 Hz, 3H).

(±)-(1,2-Bis(diphenylphosphino)ethane)(2-methyl-3-phthalimido-2-oxo-1-oxabutane-1,4-diyl)nickel (*cis*-6 and *trans*-6).

A solution of (±)-*N*-phthaloylglutamic anhydride (**4**) (311 mg, 1.20 mmol) and bpy (295 mg, 1.89 mmol) in THF (18 mL) was added over $Ni(COD)_2$ (520 mg, 1.89 mmol). The reaction mixture was stirred at 23 °C for 1 h and at 45 °C for 2 h. The resulting dark red suspension was treated with a solution of dppe (753 mg, 1.89 mmol) in CH_2Cl_2 (12 mL). The mixture was stirred at 23 °C for 4.5 h to yield a yellow suspension. The yellow solid was filtered off and washed with Et_2O to give a 1.3:1 mixture of *trans*- and *cis*-**6** (30-40 % yield). Evaporation of the filtrate led to Ni(dppe)$(CO)_2$ as an oil: IR (Nujol) 2001, 1940 cm^{-1}.[20]

6: IR (Nujol) 1710, 1650, 1380, 1100, 745, 715, 690 cm^{-1}. *trans*-**6**: ^1H NMR (300 MHz, $CDCl_3$) δ 8.15-7.24 (m, 24H), 5.37 (d, J = 5.9 Hz, 1H), 2.55-1.60 (m, 5H), 0.56 (m, 3H; $^1H\{^{31}P\}$ d, J = 7.2 Hz); $^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$) δ 57.83 (br s, 1P), 35.82 (br s, 1P). *cis*-**6**: ^1H NMR (300 MHz, $CDCl_3$) δ 8.15-7.24 (m, 24H), 4.73 (dd, J = 10.2, 3.6 Hz, 1H), 2.55-1.60 (m, 5H), 0.41-0.34 (m, 3H; $^1H\{^{31}P\}$ d, J = 6.7 Hz). $^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$) δ 57.12 (br s, 1P), 34.22 (d, J = 1.6 Hz, 1P). Carbonylation of the above mixture of *trans*-**6** and *cis*-**6** in $CDCl_3$ afforded a 2:1 mixture of anhydrides **13** and **20**. Anhydride **20**: ^1H NMR (300 MHz, DMSO-d_6) δ 7.97-7.89 (m, 4H), 5.55 (d, J = 10.6 Hz, 1H), 3.77 (dq, J = 10.6, 7.3 Hz,

1H), 1.06 (d, J = 7.3 Hz, 3H). Similarly reaction with *tert*-butyl isocyanide, followed by acid hydrolysis gave a 2:1 mixture of **9** and **10**.

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References

1. Halpern, J. *Science (Washington, D.C.)* **1985**, *227*, 869.

2. Dowd, P.; Choi, S.-C.; Duah, F., Faufman, C. *Tetrahedron* **1988**, *44*, 2137. See also: Dowd, P.; Wilk, B.; Wilk, B. K. *J. Am. Chem. Soc.* **1992**, *114*, 7949, and references cited therein:

3. Barker, H. A.; Smyth, R. D.; Weissbach, H.; Munch-Petersen, A.; Toohey, J. I.; Ladd, J. N.; Volcani, B. E.; Wilson, R. M. *J. Biol. Chem.* **1960**, *235*, 181.

4. For a different enzymatic synthesis, see: Gani, D.; Hitchcock, P. B.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1363, and references cited therein.

5. For the synthesis of the *threo* isomer as a racemate: Moiré, K.; Nomi, H.; Chuman, T.; Kohno, M.; Kato, K.; Noguchi, M. *Tetrahedron* **1982**, *38*, 3705.

6. Schmitz, F. J.; Yasumoto, T. *J. Nat. Prod.* **1991**, *54*, 1469.

7. Rinehart, K. L.; Harada, K.-I.; Namikoshi, M.; Chen, C.; Harvis, C. A.; Munro, M. H.; Blut, J. W.; Mulligan, P. E.; Beasley, V. R.; Dahlem, A. M.; Carmichael, W. W. *J. Am. Chem. Soc.* **1988**, *110*, 8557.

8. Silva, E. D.; Williams, D. E.; Andersen, R. J.; Klix, H.; Holmes, C. F. B.; Allen, T. M. *Tetrahedron Lett.* **1992**, *33*, 1561.

9. Namikoshi, M.; Rinehart, K. L.; Sakai, R.; Sivonen, K.; Carmichael, W. W. *J. Org. Chem.* **1990**, *55*, 6135. Painuli, P.; Perez, R.; Fukai, T.; Shimizu, Y. *Tetrahedron Lett.* **1988**, *29*, 11. Botes, D. P.; Wessels, P. L.; Kruger, H.; Runnegar, M. T. C.; Santikarn, S.; Smith, R. J.; Barna, J. C. J.; Williams, D. H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2747. Botes, D. P.; Tuinman, A. A.; Wessels, P. L.; Viljoen, C. C.; Kruger, H.; Williams, D. H.; Santikarn, S.; Smith, R. J.; Hammond, S. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2311.

10. See also: Choi, B. W.; Namikoshi, M.; Sun, F.; Rinehart, K. L.; Carmichael, W. W.; Kaup, A. M.; Evans, W. R.; Beasley, V. R. *Tetrahedron Lett.* **1993**, *34*, 7881.

11. For the synthesis of 3-methylaspartic acids from *L*-aspartic acid, see: Seebach, D.; Wasmuth, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 971. Wolf, J.-P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 3164.

Namikoshi, M.; Rinehart, K. L.; Dahlem, A. M.; Beasley, V. R.; Carmichael, W. W. *Tetrahedron Lett.* **1989**, *30*, 4349.

12. For related alkylations of aspartic acid enolates, see: Baldwin, J. E.; Maloney, M. G.; North, M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 833. Baldwin, J. E.; Maloney, M. G.; North, M. *Tetrahedron* **1989**, *45*, 6309. Baldwin, J. E.; Maloney, M. G.; North, M. *Tetrahedron* **1989**, *45*, 6319. Baldwin, J. E.; Adlington, R. M.; Gollins, D. W.; Sohofield, C. J. *J. Chem. Soc., Chem. Commun.* **1990**, 720.

13. Abbreviations: *(Ligands)* COD = 1,5-cyclooctadiene; bpy = 2,2'-bipyridine; Me_2Phen = 2,9-dimethyl-1,10-phenanthroline; dppe = 1,2-bis(diphenylphosphino)ethane; *(N-protective groups)* Pht = phthaloyl.

14. Castaño, A. M.; Echavarren, A. M. *Tetrahedron Lett.* **1990**, *31*, 4783.

15. Castaño, A. M.; Echavarren, A. M. *Organometallics* **1994**, *13*, 2262.

16. Sano, K.; Yamamoto, T.; Yamamoto, A. *Chem. Lett.* **1984**, 941. Sano, K.; Yamamoto, T.; Yamamoto, A. *J. Am. Chem. Soc.* **1987**, *109*, 1092.

17. Preliminary communication: Castaño, A. M.; Echavarren, A. M. *Tetrahedron Lett.* **1993**, *34*, 4361.

18. Brain, F. H. *J. Chem. Soc.* **1963**, 632.

19. Behr, A. *Carbon Dioxide Activation by Metal Complexes*; Chemie: Weinheim, 1988; Chapter 3. Hoberg, H.; Ballesteros, A.; Sigan, A.; Jenat, C.; Milchereit, A. *Synthesis* **1991**, 395. Walther, D.; Braünlich, G.; Ritter, U.; Fisher, R.; Schönecker, B. In *Organic Synthesis via Organometallics*; Dötz, K. H., Hoffmann, R. W., Eds.; Vieweg, 1991.

20. Chatt, J.; Hart, F. A. *J. Chem. Soc.* **1960**, 1378.

21. Colquhoun, H. M.; Holton, J.; Thompson, D. J.; Twigg, M. V. *New Pahways for Organic Synthesis. Practical Applications of Transition Metals*; Plenum: New York; 1985; p. 389.

22. Kidd, D. A.; King, F. E. *Nature (London)* **1948**, *162*, 776.

23. Nefkens, G. H. L.; Tesser, G. I.; Nivard, R. J. F. *Rec. Trav. Chim. Pays Bas.* **1960**, *79*, 688.

24. Wünsch, E. in *Methoden der Organischen Chemie (Houben-Weyl)*; Muller, E., Ed.; Thieme: Stuttgart, 1974; Vol. 15/2, p 223.

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