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# First Trapping Reaction of N-Boc Ethyl 3,4-Dehydropyroglutamate with Cyclopentadiene

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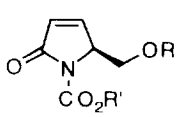
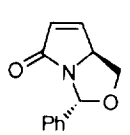
***Abstract:*** (2S)-N-Boc ethyl 3,4-dehydropyroglutamate **3**, generated *in situ* by sulfoxide elimination was trapped with cyclopentadiene in a Diels-Alder reaction giving rise the endo adduct **12** with 50% e.e. When the protecting group was removed, **V** isomerises into ethyl 2,3-dehydropyroglutamate **VI** which undergoes Diels-Alder reaction delivering the exo adduct **15**.

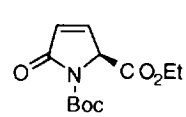
α-Amino acids have been used extensively as the starting materials for the synthesis of chiral compounds.[1,2] L-Glutamic acid is the least expensive of all the natural amino acids and because of the versatility of the γ-carboxy group it is the most used in asymmetric synthesis. Its transformation into the *N*-urethane protected pyroglutamate ester allows the selective differentiation of the carboxylic moieties present in the molecule with respect to nucleophilic[3] and electrophilic[4] attack without affecting the integrity of the pre-existing stereogenic centre. Other pyroglutamate derived substrates such as **1** and **2** (Figure 1) have been used to introduce substituents at the C-3 and/or C-4 positions *via* a Michael addition,[5] Diels-Alder,[6] epoxidation,[7] cyclopropanation[8] or hydroxylation[9] reactions.




**1**




**2**

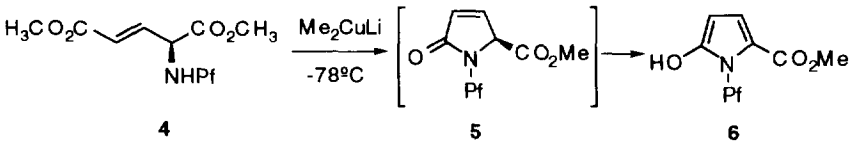



**3**

**Figure 1**

In substrates **1** and **2**[10] the pyroglutamate carboxylic functionality has been reduced to the corresponding alcohol and subsequently protected as an ether or *N,O*-acetal, in order to prevent the racemization of the pyroglutamate stereogenic centre. This necessitated the regeneration of the carboxylic group after the desired functionality has been achieved. On the other hand, there are no reports in the literature where this kind of reaction is performed with the unknown dehydropyroglutamate **3**. The only precedent regarding the reactivity of this substrate has been described by Sardina[11] in the Michael addition reaction of lithium dimethyl cuprate to the *trans* diastereoisomer of dimethyl (2S)-*N*-(9-phenylfluoren-9-yl)-3,4-dehydroglutamate **4** (Scheme 1). When this reaction is performed at low temperature, compound **4** readily aromatizes to the corresponding methyl *N*-(9-phenylfluoren-9-yl)-5-hydroxypyrrolyl-2-carboxylate **6**

through the intermediate *N*-Pf-3,4-dehydropyroglutamate ester **5**, showing the high acidity of H-2 of this later compound.

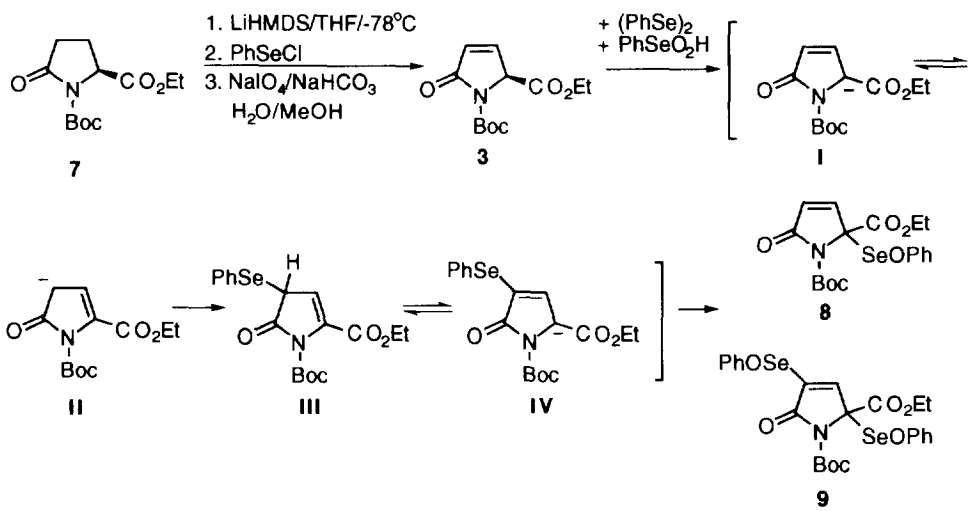



**4** **5** **6**

**Scheme 1**

Despite these precedents, we decided to explore the reactivity of compound **3** to see if an alternate protecting group on the nitrogen might improve the stability of this potentially useful intermediate.

Ethyl *N-tert*-butoxycarbonyl pyroglutamate **7** was prepared from glutamic acid following standard procedures[12]. Pyroglutamate **7** (Scheme 2) was then reacted with 2 equivalents of LiHMDS at -78°C in THF, (to avoid disubstitution and to ensure complete reaction), and then quenched with PhSeCl, yielding the corresponding selenide (60% yield) as a mixture of diastereoisomers.[4b] Oxidation of the selenide was then accomplished with $NaIO_4$ at room temperature, giving a complex mixture of products where it was possible to identify 3,4-dehydropyroglutamate **3** (30%) and the selenated derivatives **8** (10%) and **9** (5%). This reaction outcome can be explained as a result of the high acidity of H-2 in compound **3** and the generation of the electrophilic species in the reaction medium, due to the disproportionation of the PhSeOH, into $(PhSe)_2$ and $PhSeO_2H$.[13]



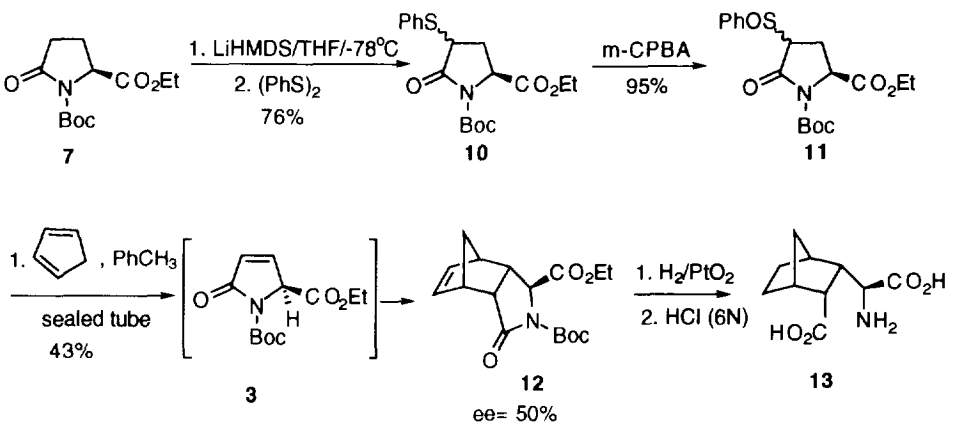

**7** **3** **I** **II** **III** **IV** **8** **9**

**Scheme 2**

After this result, pyroglutamate **7** was reacted with $(PhS)_2$ under the same reaction conditions (Scheme 3) as in the case of PhSeCl, yielding the phenylthio derivative[4b] **10** (76% yield) which was oxidized with m-CPBA into the sulfoxide **11** (95% yield). This synthetic pathway would overcome the side reactions associated with the use of selenium chemistry. On the other hand, the sulfoxide **11** is stable at room temperature, requiring thermodynamic reaction conditions for its elimination. Therefore a possibility

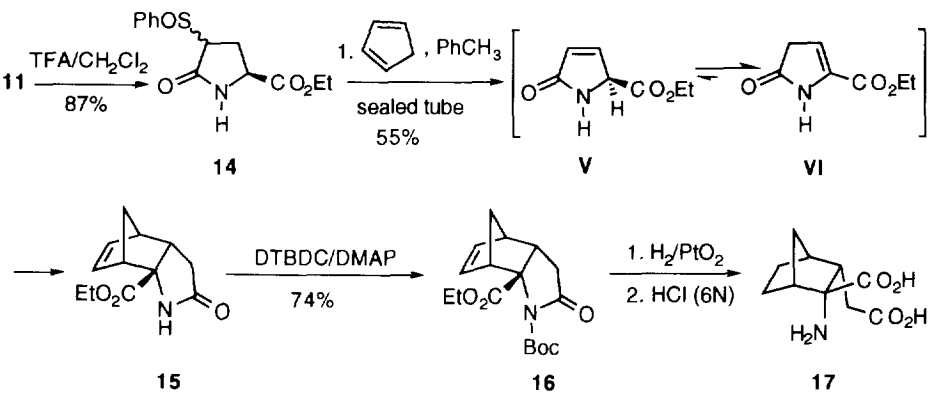
was open for the isolation of **3** or its trapping with a suitable diene in a Diels-Alder reaction, avoiding the predicted aromatization shown by Sardina[11] (Scheme 1)

Thus, when the sulphoxide **11** was heated in toluene, to carry out the *syn*-elimination, the dehydropyroglutamate **3** was obtained as the only product in the reaction mixture ($^1$H-NMR analysis of the reaction crude product). However, the isolation of this compound was problematic and the isolated yield dropped dramatically due to decomposition during chromatography. Furthermore, **3** readily racemized making it impossible to isolate in enantiomerically pure sample. The high acidity of H-2 was shown by the complete deuteration of the C-2 position in two hours and the loss of the optical rotation on standing.




**Scheme 3**

Therefore, we decided not to isolate **3** but instead to generate it *in situ* from compound **11** and then trap it in a Diels-Alder reaction with cyclopentadiene. This reaction worked well when a toluene solution of **11** was heated at 100°C in a sealed tube for 4.5 hours. The endo adduct **12** was the only one isolated showing that the reaction had taken place mainly on the less hindered face of **3**[14] . Due to the observed rapid epimerisation of **3**, it was necessary to check the enantiomeric purity of adduct **12**. The enantiomeric excess was found to be 50% by using chiral shift reagent Eu(tfc)$_3$[15] ($^1$H-NMR analysis).




**Scheme 4**

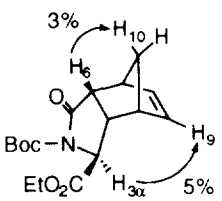
In order to improve the ee of the trapping reaction of **3**, we considered removing the protecting group on the pyroglutamate nitrogen, as a way of reducing the acidity of H-2. Thus, **11** was *N*-deprotected with TFA delivering the diastereomeric mixture **14** which was subjected to the above conditions for the Diels-Alder reaction (Scheme 4).

Surprisingly, the Diels-Alder adduct **15** (55% yield) is formed from the dienophile intermediate **VI**. This intermediate **VI** comes from the isomerization of the dehydropyroglutamate **V**, being more reactive in the cycloaddition reaction. Interestingly only the exo adduct was isolated. Finally **15** was protected with *tert*-butoxycarbonyl in order to directly compare the spectroscopic data with those of adduct **12**.

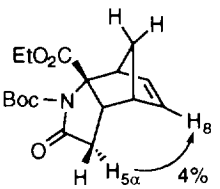
The stereochemistry of adducts **12** and **16** was assigned by a series of nOe experiments (Figure 2). The irradiation of $H_{3\alpha}$ ($\delta$ 3.94 ppm) in **12** gave a substantial nOe (5%) with $H_9$. On the other hand, $H_{10}$ ($\delta$ 1.35 ppm) displayed a 3% nOe enhancement when $H_6$ ($\delta$ 3.17 ppm) was irradiated. These experimental results confirmed the endo arrangement of the pyroglutamate ring, as well as the stereochemistry of the C-3 position of the tricyclic system.

The exo stereoselectivity of compound **16** was established by the observed 4% nOe enhancement of $H_8$, when $H_{5\alpha}$ was irradiated.

Finally, **12** and **16** were hydrogenated ($H_2/PtO_2$) and hydrolyzed to the corresponding acidic $\alpha$-amino acids **13** and **17** with 6N HCl under reflux.




**12**




**16**

**Figure 2**

In summary, though the literature precedents for (2S) N-Boc ethyl 3,4- dehydropyroglutamate **3** were not very encouraging, we have demonstrated that it is possible to trap it, in a Diels-Alder reaction with cyclopentadiene in 50% ee. This cycloaddition reaction has been restricted to cyclopentadiene, as with other dienes such as cyclohexadiene or 2,3-dimethyl butadiene the reaction does not take place obtaining polymeric material. The presence of the urethane protecting group in **3** is necessary in this process otherwise, the more reactive intermediate **VI** gave rise to the *exo* adduct **15**.

**ACKNOWLEDGEMENTS:** This research was supported by a **CDTI** programme (Plan concertado 94/0036) and the Spanish **Farma III** programme (Ministerio de Industria y Ministerio de Sanidad). I. C. is grateful to Ministerio de Educación for a Doctoral fellowship.

## EXPERIMENTAL SECTION

All solvents and reagents were purchased from commercial sources and used as recived, unless otherwise indicated. $^1$H-NMR and $^{13}$C-NMR data were recorded on a Bruker AC-200P (200 MHz). IR spectra were obtained using a Nicolet 510 P-FT (film and KBr). Melting points were determined on a Buchi 565 apparatus and are not corrected. Optical rotations were measured with a Perkin-Elmer 241

polarimeter. TLC analyses were carried out by using Merck aluminium sheets precoated with silica gel 60 $F_{254}$ (UV, 254 nm and anisaldehyde). Chromatographic separations were performed using 230-400 mesh silica gel (Merck). Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under argon. Elemental analyses were performed by the Universidad Complutense Analytical Centre (Facultad de Farmacia) Madrid.

**Procedure for the isolation of selenoxides (8), (9) and Ethyl (2S)-*N-tert*-butoxycarbonyl-3, 4-dehydro pyroglutamate (3) from Ethyl-*N-tert*-butoxycarbonyl)-4-phenylselenyl pyroglutamate.**

To a solution of the diastereomeric mixture of ethyl-*N-tert*-butoxycarbonyl)-4-phenylselenyl pyroglutamate[4b] (158 mg, 0.383 mmol) in methanol (10 mL) was added $H_2O$ (1.7 mL), $NaHCO_3$ (35 mg) and $NaIO_4$ (105 mg) with vigorous stirring. After 90 min. at room temperature, the reaction mixture was poured into 15% ether-pentane(5 mL) and saturated $NaHCO_3$ solution (5 mL). The organic layer was washed with $H_2O$ and brine. The organic layer was dried over $Na_2SO_4$ and evaporated to dryness. Finally the oily residue was purified by flash chromatography (hexane/ethyl acetate: 3/2) isolating **9** (11 mg, 5% yield), **8** (16 mg, 10 %yield) and **3** (30 mg, 30% yield).

For **8**: $^1$H NMR ($CDCl_3$) δ 7.40–7.23 (m, 5H), 6.97 (d, J = 5.7 Hz, 1H), 5.66 (d, J = 5.7 Hz, 1H), 4.29-4.11 (m, 2H), 1.59 (s, 9H), 1.32-1.20 (m, 3H). $^{13}$C NMR ($CDCl_3$) δ 170.0, 164.9, 148.2, 147.4, 138.3, 130.1, 129.0, 125.3, 123.3, 84.6, 73.2, 63.4, 28.0, 13.9.

For **9**: $^1$H NMR ($CDCl_3$) δ 7.47–7.30 (m, 10H), 6.11 (s, 1H), 4.21 (q, J = 7.1 Hz, 2H), 4.16 (q, J = 7.1 Hz, 2H), 1.57 (s, 9H), 1.23 (t, J = 7.1 Hz, 3H). $^{13}$C NMR ($CDCl_3$) δ 166.4, 164.7, 147.4, 138.5, 138.1, 136.0, 132.4, 130.1, 129.9, 129.4, 129.0, 125.3, 124.1, 84.4, 72.9, 63.3, 28.0, 13.9.

**Ethyl-*N-tert*-butoxycarbonyl)-4-phenylsulfinyl pyroglutamate (11).** To a solution of the diastereomeric mixture **10**[4b] (450 mg, 1.23 mmol) in $CHCl_3$ (20 mL) at 0ºC 80% m-CPBA (266 mg, 1.23 mmol) were slowly added and stirred at this temperature for 1 h and then an additional hour at room temperature. The reaction mixture was washed with sat. $NaHCO_3$ aq. (3x10 mL). The combined organic phases were dried over $Na_2SO_4$, filtered and evaporated to dryness. The mixture of four diastereomers (446 mg, 95%) was used without further purification.

**Ethyl (2S)-*N-tert*-butoxycarbonyl-3, 4-dehydro pyroglutamate (3).** A solution of **11** (198 mg, 0.52 mmol) in toluene (8 mL) was heated at 110ºC for 2 h. The solution was evaporated under reduced pressure and the residue purified by flash chromatograpy (hexane/ethyl acetate: 3/2) to yield 50 mg (38%) of pure compound **3** as an oil: $^1$H NMR ($CDCl_3$) δ 7.05 (dd, J = 2.4, 6.1 Hz, 1H), 6.20 (dd, J = 2.2, 6.1 Hz, 1H), 5.12 (t, J = 2.1 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 1.49 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H). $^{13}$C NMR ($CDCl_3$) δ 168.1, 166.4, 148.4, 142.8, 128.9, 83.6, 64.6, 62.4, 27.9 (3C), 14.1. IR (film) 2990, 1786, 1748, 1717, 1331 $cm^{-1}$.

**Ethyl (1R, 2S, 3S, 6R, 7S)-*N-tert*-butoxycarbonyl)-5-oxo-4-azatricyclo[5.2.1.0$^{2,6}$]-decan-8-en-3-yl carboxylate (12).** To a solution of the diastereomeric mixture **11** (1 g, 2.62 mmol) in toluene (1 mL) freshly distilled cyclopentadiene (1 mL, 6 equiv.) was added and the resulting solution heated at 100ºC for 4.5 h in a sealed tube. The reaction mixture was concentrated in *vacuo* and the residue purified by flash

chromatography using ethyl acetate/hexane (1/4) as eluent to yield 390 mg (46%) of pure **12** as an oil:$[\alpha]_D$ = -49.0 (c = 0.88, $CHCl_3$) (50% ee). $^1H$ NMR ($CDCl_3$) δ 6.28 (dd, J = 2.9, 5.7 Hz, 1H), 6.18 (dd, J = 2.9, 5.6 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.94 (d, J = 3.0 Hz, 1H), 3.33 (m, 1H), 3.22 (m, 2H), 3.17 (ddd, J = 2.8, 4.0, 9.4 Hz, 1H), 1.60 (dt, J = 1.7, 8.7 Hz, 1H), 1.42 (s, 9H), 1.35 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H). $^{13}C$ NMR ($CDCl_3$) δ 174.2, 171.4, 148.8, 137.3, 133.2, 83.3, 61.55, 61.46, 50.7, 50.0, 46.4, 45.9, 38.8, 27.7 (3C), 14.1. IR (film) 2950, 1790, 1713, 1371, 1159 $cm^{-1}$. Anal. Calcd. for $C_{17}H_{23}NO_5$: C, 63.34; H, 7.50; N, 4.34. Found: C, 63.09; H, 7.53; N, 4.50.

**Ethyl-4-phenylsulfinyl pyroglutamate (14)**. To a solution of diastereomeric mixture **11** (1.50 g, 3.93 mmol) in dry $CH_2Cl_2$ (20 mL) at 0°C was added TFA (1.5 mL, 5 equiv.). The resulting solution was stirred overnight at room temperature. The reaction mixture was washed with sat. $NaHCO_3$ aq. (3x10 mL). The combined organic phases dried over $Na_2SO_4$, filtered and evaporated to dryness to yield a mixture of the four diastereomers **14** (955mg, 86%). This mixture was used without further purification.

**(±) Ethyl (1S, 2S, 6S, 7R)-4-oxo-3-azatricyclo[5.2.1.$0^{2,6}$]-decan-8-en-2-yl carboxylate (15)**. To a solution of the diastereomeric mixture **14** (955 mg, 3.39 mmol) in toluene (1 mL) was added (freshly distilled cyclopentadiene (1.35 mL, 6 equiv.) and the resulting solution heated at 100°C for 4.5 h in a sealed tube. The reaction mixture was concentrated in *vacuo* and the residue purified by flash chromatography using ethyl acetate as eluent to yield 402 mg (53%) of pure **15** which was crystallised from ethyl acetate/hexane: M.p. 103-4°C. $^1H$ NMR ($CDCl_3$) δ 6.46 (bs, 1H), 6.27 (dd, J = 3.0, 5.7 Hz, 1H), 6.13 (dd, J = 3.0, 5.7 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.18-2.99 (m, 3H), 2.45-2.32 (m, 1H), 1.85-1.65 (m, 2H), 1.55 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H). $^{13}C$ NMR ($CDCl_3$) δ 177.7, 172.9, 136.1, 135.7, 72.4, 61.7, 51.0, 47.5, 46.1, 42.8, 33.5, 14.1. IR (KBr pellet) 3179, 2975, 1726, 1694, 1250, 1050 $cm^{-1}$. Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.69; H, 6.66; N, 6.29.

**(±) Ethyl (1S, 2S, 6S, 7R)-*N-tert*-butoxycarbonyl)-4-oxo-3-azatricyclo[5.2.1.$0^{2,6}$]-decan-8-en-2-yl carboxylate (16)**. To a solution of **15** (66 mg, 0.30 mmol) in $CH_2Cl_2$ (1 mL) were added triethylamine (42 µl, 0.30 mmol), di-*tert*-butyl dicarbonate (130 mg, 0.60 mmol) and 4-dimethylamino pyridine (36 mg, 0.30 mmol). The resulting solution was stirred for 4 h at room temperature under a nitrogen atmosphere. The volatiles were removed, and the residue purified by flash chromatography using ethyl acetate/hexane (1/3) as eluent to yield 71 mg (74%) as an oil: $^1H$ NMR ($CDCl_3$) δ 6.24 (dd, J = 2.9, 5.7 Hz, 1H), 6.08 (dd, J = 3.1, 5.7 Hz, 1H), 4.18 (dq, J = 4.5, 7.1 Hz, 2H), 3.59 (bs, 1H), 2.93 (bs, 1H), 2.70-2.52 (m, 2H), 2.06 (m, 1H), 1.85 (m, 1H), 1.73 (m, 1H), 1.47 (s, 9H), 1.24 (t, J = 7.1 Hz, 3H). $^{13}C$ NMR ($CDCl_3$) δ 174.6, 172.6, 148.8, 137.1, 135.8, 83.4, 75.1, 61.6, 50.0, 48.7, 45.9, 41.7, 34.9, 27.8 (3C), 14.1. IR (KBr pellet) 1740, 1751, 1709, 1292 $cm^{-1}$. Anal. Calcd. for $C_{17}H_{23}NO_5$: C, 63.34 H, 7.50; N, 4.34. Found: C, 63.10; H, 7.57; N, 4.30.

**Endo-2-amino-2-(3-caboxybicyclo[2.2.1]heptan-2-yl) acetic acid, hydrochloride (13).** To a solution of **12** (1 mmol) in 5 ml of ethyl acetate was added platinum (IV) oxide (0.1 mmol). Reaction was allowed to proceed under hydrogen atmosphere at r.t. overnight. Filtration of the catalyst through celite and evaporation of the solvent gave a solid which was crystallized from hexane. Finally it was hydrolysed under reflux overnight with 6N HCl solution (15 ml). Evaporation of the solvent to dryness and trituration of the solid with acetone gave the hydrocloride **13**. M.p. 216-7°C. $^1H$ NMR ($CD_3OD$) δ 3.99 (br s, 1H), 2.83-2.75 (m, 2H), 2.52-2.47 (m, 2H), 1.55-1.39 (m, 6H). $^{13}C$ NMR ($CD_3OD$) δ 181.7, 176.7, 57.1, 48.9,

47.2, 42.2, 41.7, 40.0, 25.8, 23.1. IR (KBr pellet) 3451, 1719, 1653, 1647 $cm^{-1}$. Anal. Calcd. for $C_{10}H_{16}ClNO_4$: C, 48.10; H, 6.46; N, 5.61. Found: C, 48.21; H, 6.40; N, 5.52.

**Exo-3-amino-3-caboxybicyclo[2.2.1]heptan-2-yl acetic acid, hydrochloride (17).** To a solution of **16** (1 mmol) in 5 ml of ethyl acetate was added platinum (IV) oxide (0.1 mmol). Reaction was allowed to proceed under hydrogen atmosphere at r.t. overnight. Filtration of the catalyst through celite and evaporation of the solvent gave a solid which was crystallized from AcOEt/hexane. Finally it was hydrolysed under reflux overnight with 6N HCl solution (15 ml). Evaporation of the solvent to dryness and trituration of the solid with acetone gave the hydrocloride **17** M.p. >230ºC. $^1H$ NMR (DMSO-$d_6$) δ 2.88-2.79 (m, 1H), 2.60 (br s, 1H), 2.49 and 2.23 (AB part of ABX system, $J_{AB}$ = 18.2 Hz, $J_{AX}$ = 10.1 Hz, $J_{BX}$ = 2.6 Hz, 2H), 2.32 (m, 1H), 1.90-1.85 (m, 1H), 1.61-1.26 (m, 5H). $^{13}C$ NMR (DMSO-$d_6$) δ 178.1, 176.8, 70.6, 70.5, 45.1, 44.8, 41.0, 40.3, 32.2, 24.9, 21.8. IR (KBr pellet) 3316, 2959, 2886, 1709, 1638, 1233 $cm^{-1}$. Anal. Calcd. for $C_{10}H_{16}ClNO_4$: C, 48.10; H, 6.46; N, 5.61. Found: C, 48.02; H, 6.51; N, 5.73.

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