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Regioselective opening of *N*-Cbz glutamic and aspartic anhydrides with carbon nucleophiles

Geoffrey Deguest, Laurent Bischoff,* Corinne Fruit and Francis Marsais

Laboratoire de Chimie Organique Fine et Hétérocyclique—IRCOF-INSA Rouen—CNRS UMR 6014—BP 08, 76131 Mont-Saint-Aignan Cedex, France

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Abstract—Depending on the experimental conditions, aspartic and glutamic anhydrides can be opened regioselectively with Grignard reagents, thus giving access to different isomers of chiral amino-ketoesters.

1. Introduction

Glutamic and aspartic acid derivatives are both widely used in synthesis, owing to the possible differentiation between the two carboxylic acids. Generally, these different reactivities constitute a valuable tool in selective protection. This implies that selective activation of a carboxylic acid moiety is consecutive to the protection of the other acid, thus generally requiring two or three steps to reach a suitably protected-activated derivative from the starting diacid.

Herein, we report short and efficient syntheses of amino-ketoesters starting from *N*-Cbz glutamic and aspartic anhydrides. These synthons can lead to regioselective nucleophilic attack by organometallics, or to rapid transformations which reverse the regioselectivity without prior monoprotection.

2. Results and discussion

2.1. Regioselective α-opening

In the title anhydrides, the presence of the N-protected amino group is able to activate the neighboring carbonyl, thus affording regioselective attack by alcohols[1] or amines[2] due to an intramolecular hydrogen bond. Furthermore, $NaBH_4$ can also reduce regioselectively the α-carbonyl, providing the corresponding lactone after intramolecular esterification.[3]

The literature provides two main methods for the synthesis of aminoketones from such compounds. On the one hand, the internal anhydride can be used as a powerful electrophile under Friedel–Crafts conditions (i.e., $AlCl_3$ in the presence of electron-rich aromatic substances), leading to an attack on the side-chain carbonyl.[4] On the other hand, the reaction of strongly basic organometallics generally requires protected amino acids, often expensive or time-consuming, the anhydrides being used as precursors of suitably protected synthons. While nucleophilic additions to these anhydrides are well-known, reactions involving organometallics are sparse. Only aspartic anhydride was reacted with organomagnesiums in refluxing ether, affording double addition at the α-carbon with low yields of the resulting lactones.[5]

In order to develop very short syntheses of amino-ketoesters from both anhydrides, we examined the reactivities of different organometallics (Scheme 1). Aryl or alkyllithiums were first reacted with glutamic anhydride (prepared by dehydration of glutamic acid with acetic anhydride).[6] The reaction of such organometallics mostly resulted in competitive deprotonation of the carbamate, to give pyroglutamic acid **4** (Table 1, entries 1 and 2). Traces of the desired α-amino-ketoacid **2** were observed with phenyllithium, along with 21% of the isomeric γ-aminoketone **3**, presumably obtained by the subsequent opening of lithium pyroglutamate formed in situ. Each experiment also

* Corresponding author. Fax: +33 2 35 52 29 62; e-mail: laurent.bischoff@insa-rouen.fr

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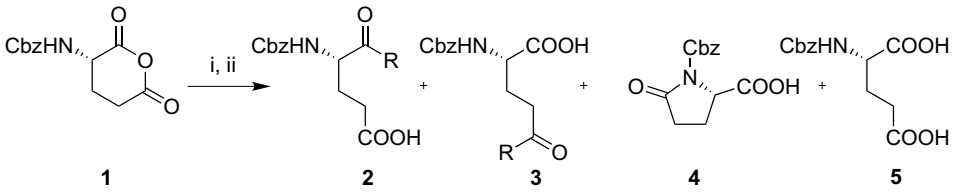


Scheme 1. Reagents and conditions: (i) 1.6 equiv, R–M, THF; (ii) 0.5 M citric acid.

Table 1. Reaction of different organometallics with glutamic anhydride **1**

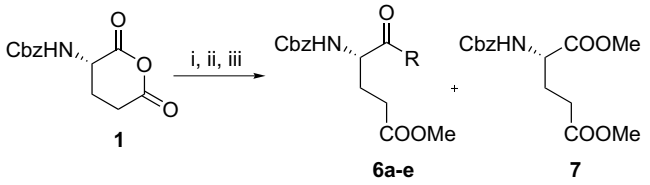
Entry	R–M	Conditions	**2** (%)	**3** (%)	**4** (%)	**5** (%)
1	PhLi	−78 °C, 4 h	6	21	37	36
2	*n*-BuLi	−78 °C, 2 h	0	0	52	48
3	*t*-BuMgCl	−78 °C, 4 h	0	0	65	35
4	PhZnCl	−78 °C, 2 h	0	0	15	85
5	PhMgCl	−78 °C, 4 h	**63**	**0**	**21**	**16**
6	Ph_3MgLi	−78 °C to rt then rt 2 h	17	26	18	39

Percentages were estimated by NMR on the crude material spectra.

afforded non-negligible amounts of *N*-Cbz glutamic acid **5**, resulting from hydrolysis of the remaining anhydride or its salts. Using a more basic alkyllithium reagent, such as butyllithium, confirmed the predominant formation of pyroglutamic acid **4** which, however, did not further react in this case. This was confirmed with *t*-BuMgCl, which exhibited a very low nucleophilicity, and also led to the formation of **4** in 65% yield, without further addition. As we wished to lower the basicity of the organometallic, PhZnCl was used. No ketone was observed in this experiment and higher temperatures resulted in degradation.

We were pleased to note that the reaction of the organomagnesium species (entry 5) led to a regioselective opening of the anhydride at the α-carbon. Concomitant formation of pyroglutamic acid **4** and glutamic acid **5** was also observed. Higher temperatures resulted in more pyroglutamic acid **4**, while other solvents such as ether or toluene, made the addition much slower without increasing the yields. We attempted to use a lithium magnesiate[7] but this led to a non-regioselective reaction, presumably due to the more basic character of this reagent.

We then extended the reactivity of glutamic anhydride to other Grignard reagents (Scheme 2, Table 2). In order to avoid difficulties in separating the ketoacid from *N*-Cbz glutamic acid **5**, the opening was followed by an esterification of the crude reaction mixture. Only the keto ester **6a** and *N*-Cbz-glutamic acid diester **7** were thus obtained, *N*-



Scheme 2. Reagents and conditions: (i) RMgX, −78 °C, THF; (ii) 0.5 M citric acid; (iii) MeOH, $SOCl_2$, overnight.

Table 2. Opening glutamic anhydride with Grignard reagents

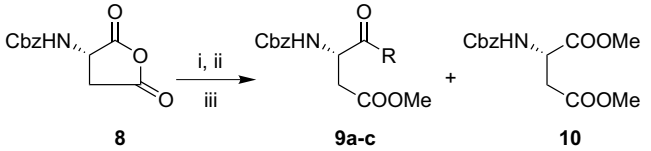
Entry	Organometallic	Compound no.	Yield[a] (%)
1	PhMgCl	**6a**	57
2	3-(MeO)-C_6H_4-MgBr	**6b**	63
3	2-Thienyl-MgBr	**6c**	58
4	*n*-BuMgBr	**6d**	45
5	*n*-Hexyl-MgBr	**6e**	46

[a] Isolated yields after column chromatography.

Cbz pyroglutamic acid was also transformed into diester **7**. When applying our experimental conditions (i.e. 1.6 M equiv of RMgX in THF, −78 °C, 4 h), we observed that arylmagnesium reagents could provide α-amino arylketones **6a**–**c** in 57–63% isolated yields (entries 1–3). We also obtained ketone **6b**, which can not be synthesized via Friedel–Crafts acylation, making our method a complementary tool for such preparations.

Alkylmagnesium halides gave similar aminoketones with modest yields after subsequent esterification (entries 4 and 5).

In order to broaden the scope of the synthesis of aminoketones, we applied this procedure to aspartic anhydride (Scheme 3). As expected, the same regioselective opening occurred with comparable yields of α-aminoketones **9a**–**c** (Table 3). Since this substrate is unable to provide internal imides by an intramolecular process, the diacid was the only side product, isolated as its diester derivative **10**.



Scheme 3. Reagents and conditions: (i) 1.6 equiv RMgX, THF, − 78 °C; (ii) 0.5 M citric acid; (iii) MeOH, $SOCl_2$, overnight.

Table 3. Opening aspartic anhydride with Grignard reagents

Entry	Reagent	Compound	Yield[a] (%)
1	PhMgCl	**9a**	54
2	3-(MeO)-C_6H_4-MgBr	**9b**	60
3	*n*-BuMgBr	**9c**	41

[a] Isolated yields after column chromatography.

In summary, regioselective nucleophilic additions of organomagnesium compounds on aspartic and glutamic

anhydrides provide a very expeditious method for the preparation of β-amino-γ-ketoesters and particularly γ-amino-δ-ketoesters.

2.2. Addition onto the side-chain carbonyl

In the literature, regioselectivity in favor of the γ-amino-ketone is generally obtained by the use of pyroglutamic esters,[8] a method of choice for the preparation of 5-substituted prolines. These pyroglutamic esters are most classically obtained via treatment of glutamic anhydride in the presence of dicyclohexylamine.[9] In the present study, the α-amino-γ-ketoacid **3** was obtained using more basic reagents such as PhLi or Ph_3MgLi (Table 1). We then tried to preform the pyroglutamate intermediate in situ by action of a basic organomagnesium (Scheme 4).

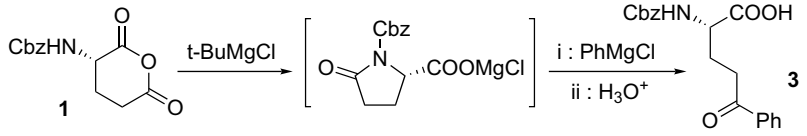
Thus, the reaction of *t*-BuMgCl, followed by the addition of PhMgCl gave a 1:10 ratio of α:γ-ketones with a global 38% conversion, along with 25% unreacted pyroglutamic acid **4** and 37% glutamic acid **5**. This poor conversion can be explained by the pyroglutamate being a poor electrophile, since the latter is formed as its magnesium salt, which is much less reactive than pyroglutamic esters themselves.

We thought that the most efficient way of reversing the regioselectivity was to prevent the hydrogen bond activation by the carbamate, accounting for the α-regioselectivity. For this purpose, total N-protection as a dicarbamate was attempted. Thus, anhydride **1** was treated with Boc_2O in the presence of 10% DMAP. To our great surprise, these conditions allowed a very clean formation of *tert*-butyl-*N*-Cbz-pyroglutamate **11** (Scheme 5). In addition, Boc_2O itself is likely to induce dehydration of the diacid, thus making it suitable for the formation of *N*-Cbz glutamic acid internal anhydride **1**. This was confirmed by using *N*-Cbz glutamic acid in the presence of one more molar equivalent of Boc_2O. In this way, side reactions could be avoided if nucleophilic reagents were further allowed to react with the resulting material.

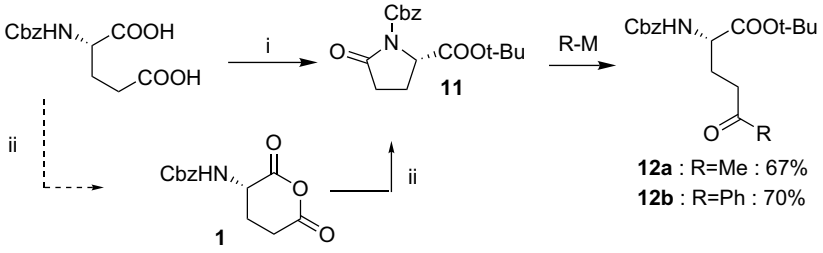
A very short procedure first involved the treatment of *N*-Cbz glutamic acid with Boc_2O/DMAP. Subsequent evaporation afforded clean pyroglutamate **11** which could be treated with Grignard reagents[8] without further purification. Opening **11** with CH_3MgBr or PhMgCl gave the α-amino-γ-ketoesters **12a** and **12b** in 67% and 70% yields, respectively (Scheme 5). The enantiomeric excess measured for **12a** was consistent with that previously reported.[10]

To the best of our knowledge, this constitutes the shortest synthesis of N-protected pyroglutamic esters, since these compounds are generally prepared in three to four steps. Under our conditions, only one step is required to achieve at the same time, side-chain activation and α-acid protection. This preparation can be conducted on a multigram scale, making it a valuable tool in synthesis of pyrrolidine precursors.

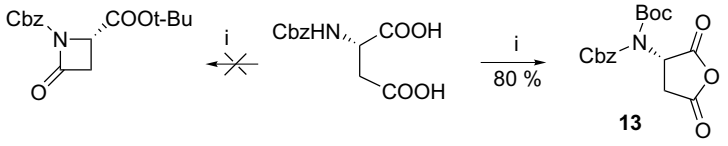
With these conditions in hand, we attempted to apply them to aspartic anhydride, although we believed that its geometry would prevent the intramolecular acylation of the nitrogen. As depicted in Scheme 6, treatment of *N*-Cbz aspartic acid with Boc_2O led to the *N*,*N*-dicarbamate **13** instead of the azetidinone.



Scheme 4. Attempt at reversing the regioselectivity.



Scheme 5. Reagents and conditions: (i) 2 equiv Boc_2O, cat DMAP; (ii) 1 equiv Boc_2O, cat DMAP.



Scheme 6. Reagents and conditions: (i) 2 equiv Boc_2O, cat DMAP.

When subjected to reaction with phenylmagnesium chloride, this anhydride may have led to nucleophilic attack onto the β-carbon. However, the purification of the resulting compound was sluggish and did not allow us to make reliable conclusions.

Even though the synthetic applications of N,N-diprotected aspartic anhydride **13** are limited, the straight formation of pyroglutamate **11** from N-protected glutamic acid makes it a very useful tool in synthesis.

3. Conclusion

This work shows that the synthetic utility of aspartic and glutamic anhydrides can be advantageously extended to ketone synthesis. Chiral amino-ketoesters can be efficiently synthesized by regioselective nucleophilic addition of organomagnesiums. The wide range of applications of chiral amino ketoesters affords an interesting choice of targets in synthesis.

4. Experimental

4.1. General experimental

NMR spectra were recorded on a 300 MHz Bruker Avance. Unless otherwise indicated, all spectra were recorded at 300 MHz for ^{1}H and 75 MHz for ^{13}C in $CDCl_3$. All chemical shifts are given in ppm. R_f given for TLC analyses were measured on silica gel Merck Kieselgel F_{254} aluminum plates. Optical rotations were measured on a Perkin–Elmer 341 polarimeter.

4.1.1. Typical procedure for the synthesis of Grignard reagents. Aryl or alkyl halide (8 mmol) was added to a suspension of magnesium turnings (204 mg, 8.4 mmol) in THF (1.5 mL). The solution was stirred at 40 °C for 2 h then diluted with anhydrous THF (6.5 mL). Titration was carried out with L-(−)-menthol/1,10-phenanthroline.

4.1.2. Typical procedure for 6a–e and 9a–c. To a stirred solution of *N*-Cbz-glutamic anhydride (500 mg, 1.89 mmol) or commercially available aspartic anhydride (500 mg, 2.00 mmol) in anhydrous THF (20 mL) was added the Grignard reagent (3.03 mmol) dropwise at −78 °C over a period of 5 min. Stirring was continued for an additional 4 h at this temperature. The reaction was quenched with 0.5 M citric acid (7 mL), then warmed to rt and the crude material isolated by extractive work-up with diethyl ether. The residue was taken-up in 20 mL absolute methanol, then thionyl chloride (0.14 mL, 1.89 mmol) was added and the solution stirred overnight. After subsequent evaporation, the residue was chromatographed on silica gel.

4.1.3. Procedure for the straight synthesis of ketones 12a and 12b from *N*-Cbz glutamic acid. To a stirred solution of di-*tert*-butyl dicarbonate (776 mg, 3.56 mmol) in anhydrous THF (4 mL), was added 4-dimethylaminopyridine (22 mg, 0.18 mmol) immediately followed by *N*-Cbz glutamic acid (500 mg, 1.78 mmol) in anhydrous THF (8 mL). After stirring overnight, and subsequent evaporation, the residue was dissolved in anhydrous THF (20 mL). The Grignard reagent (2.84 mmol) was added at −78 °C and stirred for 6 h at this temperature. Quenching with 0.5 M citric acid (10 mL) and extractive work-up with diethyl ether afforded a residue, which was chromatographed on silica gel.

4.2. Data for new compounds

4.2.1. (4*S*)-Methyl 4-(benzyloxycarbonylamino)-5-oxo-5-phenylpentanoate 6a. Following the general procedure and using commercially available PhMgCl, flash chromatography on silica gel (cyclohexane–ethyl acetate 1:2, $R_f = 0.50$) provided **6a** (383 mg, 57%) as a colorless oil. ^{1}H NMR δ 1.69–1.82 (1H, m), 2.27–2.57 (3H, m), 3.66 (3H, s), 5.11 (2H, s), 5.45 (1H, td, *J* 8.3 and 3.0 Hz), 5.85 (1H, d, *J* 8.3 Hz), 7.35 (5H, m), 7.52 (2H, dd, *J* 7.5 and 7.2 Hz), 7.61 (1H, t, *J* 7.2 Hz), 8.04 (2H, d, *J* 7.5 Hz); ^{13}C NMR δ 28.9, 29.5, 51.8, 54.8, 67.1, 128.1, 128.2, 128.6, 128.9, 129.0, 134.0, 134.1, 136.3, 156.3, 173.3, 198.3; IR (cm^{-1}): 3349, 2951, 1733, 1685, 1596, 1522, 1448, 1353, 1261, 1218, 1055, 697; MS-IC(+): 356 (100%), 310, 248, 222, 205, 73; $[\alpha]_D^{20} = +29.0$ (*c* 1, CH_2Cl_2). Elemental analysis calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.55; H, 5.98; N, 3.96.

4.2.2. (4*S*)-Methyl 4-(benzyloxycarbonylamino)-5-(3-methoxyphenyl)-5-oxopentanoate 6b. Titration of 3-methoxyphenylmagnesium bromide prepared as described above, gave a concentration of 0.59 mol L^{-1}. Following the general procedure, flash chromatography on silica gel (toluene–ethyl acetate 4:1, $R_f = 0.57$) provided **6b** (459 mg, 63%) as a colorless oil. ^{1}H NMR δ 1.68–1.81 (1H, m), 2.30–2.41 (2H, m), 2.46–2.59 (1H, m), 3.67 (3H, s), 3.87 (3H, s), 5.11 (2H, s), 5.43 (1H, td, *J* 8.4 and 2.8 Hz), 5.81 (1H, d, *J* 7.9 Hz), 7.16 (1H, dd, *J* 8.1 and 2.4 Hz), 7.35 (6H, m), 7.58 (1H, s), 7.65 (1H, d, *J* 7.5 Hz); ^{13}C NMR δ 29.1, 29.5, 51.9, 54.9, 55.6, 67.2, 112.9, 120.9, 121.5, 128.2, 128.3, 128.6, 130.1, 135.3, 136.3, 156.3, 160.1, 173.3, 198.1; IR (cm^{-1}): 3338, 2945, 1726, 1684, 1596, 1521, 1435, 1300, 1260, 1248, 1044, 698; MS-IC(+): 386 (100%), 342, 282, 250, 152, 73; $[\alpha]_D^{20} = +23.6$ (*c* 1, CH_2Cl_2). Elemental analysis calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.47; H, 6.06; N, 3.54.

4.2.3. (4*S*)-Methyl 4-(benzyloxycarbonylamino)-5-oxo-5-(thiophen-2-yl)pentanoate 6c. Titration of 2-thienylmagnesium bromide prepared as described above, gave a concentration of 0.56 mol L^{-1}. Following the general procedure, flash chromatography on silica gel (toluene–ethyl acetate 4:1, $R_f = 0.47$) provided **6c** (395 mg, 58%) as a brown oil. ^{1}H NMR δ 1.77–1.89 (1H, m), 2.30–2.60 (3H, m), 3.69 (3H, s), 5.11 (2H, s), 5.28 (1H, td, *J* 8.1 and 3.2 Hz), 5.71 (1H, d, *J* 8.1 Hz), 7.19 (1H, t, *J* 4.4 Hz), 7.3 (5H, m), 7.71 (1H, d, *J* 4.4 Hz), 8.04 (1H, d, *J* 4.4 Hz); ^{13}C NMR δ 29.5, 29.6, 51.9, 55.7, 67.2, 128.2, 128.3, 128.6, 128.8, 128.9, 133.9, 135.4, 136.2, 141.1, 156.3, 173.4, 191.1; IR (cm^{-1}): 3356, 2922, 1720, 1660, 1513, 1438, 1412, 1357, 1223, 1049, 731, 698; MS-IC(+): 362 (100%), 318, 282, 250, 228, 212, 152, 107, 91; $[\alpha]_D^{25} = -423$ (*c* 1, CH_2Cl_2). Elemental analysis calcd for

$C_{18}H_{19}NO_5S$: C, 59.82; H, 5.30; N, 3.88; S, 8.87. Found: C, 59.89; H, 5.16; N, 3.86; S, 8.61.

4.2.4. (4*S*)-Methyl 4-(benzyloxycarbonylamino)-5-oxononanoate 6d. Titration of butylmagnesium bromide prepared as described above, gave a concentration of 0.54 mol L^{-1}. Following the general procedure, flash chromatography on silica gel (cyclohexane–ethyl acetate 1:1, $R_f = 0.74$) provided **6d** (285 mg, 45%) as a colorless oil. ^{1}H NMR δ 0.86–0.91 (3H, m), 1.21–1.35 (2H, m), 1.50–1.58 (2H, m), 1.72–1.86 (1H, m), 2.21–2.56 (5H, m), 3.64 (3H, s), 4.42 (1H, td, *J* 7.6 and 3.8 Hz), 5.07 (2H, s), 5.65 (1H, d, *J* 7.6 Hz), 7.33 (5H, m); ^{13}C NMR δ 13.9, 22.3, 25.6, 26.8, 29.6, 39.5, 51.9, 58.9, 67.0, 128.1, 128.3, 128.6, 136.3, 156.1, 173.3, 208.6; IR (cm^{-1}): 3348, 2957, 1731, 1714, 1519, 1455, 1254, 1175, 1028, 740, 698; MS-IC(+): 336 (100%), 292, 250, 202, 91; $[\alpha]_D^{20} = +24.4$ (*c* 1, CH_2Cl_2). Elemental analysis calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.31; H, 7.63; N, 4.13.

4.2.5. (4*S*)-Methyl 4-(benzyloxycarbonylamino)-5-oxoundecanoate 6e. Titration of hexylmagnesium bromide prepared as described above, gave a concentration of 0.54 mol L^{-1}. Following the general procedure, flash chromatography on silica gel (cyclohexane–ethyl acetate 2:1, $R_f = 0.48$) provided **6e** (316 mg, 46%) as a yellow oil. ^{1}H NMR δ 0.84–0.88 (3H, m), 1.25 (6H, m), 1.57 (2H, m), 1.77 (1H, m), 2.22–2.56 (5H, m), 3.65 (3H, s), 4.42 (1H, td, *J* 7.6 and 3.8 Hz), 5.08 (2H, s), 5.61 (1H, d, *J* 7.6 Hz), 7.33 (5H, m); ^{13}C NMR δ 14.1, 22.5, 23.5, 26.9, 28.9, 29.6, 31.6, 39.8, 51.9, 58.9, 67.1, 128.2, 128.3, 128.6, 136.3, 156.2, 173.4, 208.6; IR (cm^{-1}): 3344, 2954, 1718, 1522, 1454, 1329, 1253, 1051, 698; MS-IC(+): 364 (100%), 320, 250, 230, 91; $[\alpha]_D^{20} = +13.1$ (*c* 1, CH_2Cl_2). Elemental analysis calcd for $C_{20}H_{29}NO_5$: C, 66.09; H, 8.04; N, 3.85. Found: C, 66.07; H, 8.07; N, 3.82.

4.2.6. (3*S*)-Methyl 3-(benzyloxycarbonylamino)-4-oxo-4-phenylbutanoate 9a. Following the general procedure and using commercially available PhMgCl, flash chromatography on silica gel (cyclohexane–ethyl acetate 2:1, $R_f = 0.50$) provided **9a** (417 mg, 54%) as a colorless oil. ^{1}H NMR δ 2.75–2.82 (1H, dd, *J* 16.2 and 5.5 Hz), 2.9–2.98 (1H, dd, *J* 16.2 and 5.5 Hz), 3.64 (3H, s), 5.11 (2H, s), 5.57 (1H, td, *J* 8.5 and 5.5 Hz), 5.97 (1H, d, *J* 8.5 Hz), 7.33 (5H, m), 7.46 (2H, dd, *J* 7.5 and 7.4 Hz), 7.59 (1H, t, *J* 7.4 Hz), 7.98 (2H, d, *J* 7.5 Hz); ^{13}C NMR δ 37.1, 52.1, 52.5, 67.2, 128.1, 128.3, 128.6, 128.7, 128.9, 133.8, 134.4, 136.2, 155.7, 171.0, 197.1; MS-IC(+): 342 (100%), 298, 236, 208,191, 152, 91; $[\alpha]_D^{25} = -12.5$ (*c* 1, CH_2Cl_2). Elemental analysis calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.80; H, 5.42; N, 4.24.

4.2.7. (3*S*)-Methyl 3-(benzyloxycarbonylamino)-4-(3-methoxyphenyl)-4-oxobutanoate 9b. Titration of 3-methoxyphenylmagnesium bromide prepared as described above, gave a concentration of 0.59 mol L^{-1}. Following the general procedure, flash chromatography on silica gel (toluene–ethyl acetate 4:1, $R_f = 0.55$) provided **9b** (448 mg, 60%) as a colorless oil. ^{1}H NMR δ 2.75–2.82 (1H, dd, *J* 16.2 and 5.3 Hz), 2.91–2.98 (1H, dd, *J* 16.2 and 5.3 Hz), 3.65 (s, 3H), 3.83 (s, 3H), 5.12 (s, 2H), 5.55 (td, *J* 8.5 and 5.3 Hz), 5.93 (d, *J* 8.5 Hz), 7.12 (1H, dd, *J* 8.1 and 2.0 Hz), 7.33 (m, 6H), 7.48 (s, 1H), 7.54 (1H, d, *J* 7.5 Hz); ^{13}C NMR δ 37.2, 52.2, 52.7, 55.6, 67.3, 112.7, 120.8, 121.3, 128.1, 128.3, 128.7, 129.0, 135.7, 136.2, 155.8, 160.1, 171.1, 196.9; MS-IC(+): 372 (100%), 328, 282, 236, 221, 152, 113, 91; $[\alpha]_D^{25} = -11.6$ (*c* 1, CH_2Cl_2). Elemental analysis calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.65; H, 5.62; N, 3.89.

4.2.8. (4*S*)-Methyl 4-(benzyloxycarbonylamino)-5-oxooctanoate 9c. Titration of butylmagnesium bromide prepared as described above, gave a concentration of 0.54 mol L^{-1}. Following the general procedure, flash chromatography on silica gel (cyclohexane–ethyl acetate 2:1, $R_f = 0.52$) provided **9c** (265 mg, 41%) as a colorless oil. ^{1}H NMR δ 0.90 (3H, t, *J* 7.2 Hz), 1.25–1.32 (2H, m), 1.52–1.58 (2H, m), 2.52–2.58 (2H, m), 2.73–2.81 (1H, dd, *J* 17.1 and 4.3 Hz), 2.97–3.03 (1H, dd, *J* 17.1 and 4.3 Hz), 3.66 (3H, s), 4.49 (1H, td, *J* 8.8 and 4.52 Hz), 5.13 (2H, s), 5.88 (1H, d, *J* 8.8 Hz), 7.36 (5H, m); ^{13}C NMR δ 14.0, 22.3, 25.5, 35.7, 38.8, 52.2, 56.4, 67.3, 128.2, 128.4, 128.7, 136.2, 156.1, 171.9, 208.6; MS-IC(+): 336 (100%), 292, 250, 202, 91; $[\alpha]_D^{25} = +29.3$ (*c* 1, CH_2Cl_2). Elemental analysis calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.24; H, 7.15; N, 4.59.

4.2.9. *tert*-Butyl-*N*-Cbz pyroglutamate 11. To a stirred solution of di-*tert*-butyl dicarbonate (776 mg, 3.56 mmol) in anhydrous THF (4 mL), was added 4-dimethylaminopyridine (22 mg, 0.18 mmol) immediately followed by *N*-Cbz glutamic acid (500 mg, 1.78 mmol), diluted in 8 mL anhydrous THF. After stirring overnight, the reaction mixture was filtrated through Celite, then partitioned between diethyl ether and brine. The organic layer was dried over magnesium sulfate and evaporated to give **11** as a light brown solid (592 mg, 100%). ^{1}H NMR δ 1.31 (9H, s), 1.90–2.62 (4H, m), 4.49 (1H, dd, *J* 9.4 and 2.6 Hz), 5.21 (2H, dd, *J* 12.0 and 6.0 Hz), 7.30 (5H, m); ^{13}C NMR δ 22.3, 28.2, 31.4, 59.8, 68.8, 82.9, 128.6, 128.8, 128.9, 135.4, 170.5, 173.6; $[\alpha]_D^{21} = -39.6$ (*c* 0.05, $CHCl_3$).

4.2.10. (2*S*)-*tert*-Butyl 2-(benzyloxycarbonylamino)-5-oxohexanoate 12a.[10] Following the above procedure and using a commercially available solution of MeMgBr (3.0 M in Et_2O), chromatography on silica gel (cyclohexane–ethyl acetate 4:6, $R_f = 0.61$) provided **12a** (399 mg, 67%) as a colorless oil. ^{1}H NMR δ 1.46 (9H, s), 1.84 (1H, m), 2.13 (4H, s), 2.51 (2H, m), 4.22 (1H, m), 5.10 (2H, s), 5.40 (1H, d, *J* 7.9 Hz), 7.35 (m, 5H); ^{13}C NMR δ 207.55, 171.22, 156.09, 136.35, 128.58, 128.48, 128.24, 82.41, 66.98, 53.87, 39.36, 30.06, 28.01, 26.76; MS-IC(+): 336, 318, 302, 280, 218; $[\alpha]_D^{20} = +6.8$ (*c* 0.45, $CHCl_3$).

4.2.11. (2*S*)-*tert*-Butyl 2-(benzyloxycarbonylamino)-5-oxo-5-phenylpentanoate 12b. Following the above procedure and using a commercially available solution of PhMgCl (2.0 M in THF), chromatography on silica gel (cyclohexane–ethyl acetate 4:1, $R_f = 0.39$) provided **12b** (496 mg, 70%) as a colorless oil. ^{1}H NMR δ 1.39 (9H, s), 1.97–2.07 (1H, m), 2.18–2.29 (1H, m), 3.05 (2H, m), 4.28 (1H, m), 5.01 (2H, s), 5.41 (1H, d, *J* 7.9 Hz), 7.27 (5H, m), 7.37 (2H, t, *J* 7.3 Hz), 7.49 (1H, t, *J* 7.3 Hz), 7.85 (2H, d,

J 7.3 Hz); ^{13}C NMR δ 27.6, 28.4, 34.9, 54.4, 67.3, 82.8, 115.7, 120.7, 128.4, 128.6, 128.9, 129.0, 129.9, 133.6, 136.6, 136.9, 156.5, 171.6, 199.4; MS-IC(+): 398 (100%), 380, 342, 296, 246; $[\alpha]_D^{25} = +9.6$ (*c* 1, CH_2Cl_2). Elemental analysis calcd for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.32; H, 6.77; N, 3.68.

4.2.12. *N*-Boc, *N*-Cbz aspartic anhydride 13. To a stirred solution of di-*tert*-butyl dicarbonate (873 mg, 4.0 mmol) in 4 mL anhydrous THF, was added 4-dimethylaminopyridine (24 mg, 0.2 mmol) immediately followed by *N*-Cbz aspartic acid (500 mg, 2.00 mmol), diluted in 8 mL anhydrous THF. After stirring overnight, and after filtration and evaporation the residue was partitioned between diethyl ether and brine. The organic layer was dried over magnesium sulfate and then evaporated to give **13** (559 mg, 80%) as a light brown oil. ^{1}H NMR (DMSO) δ 1.23 (s, 9H), 2.94 (1H, dd, *J* 18.6 and 6.6 Hz), 3.16 (1H, dd, *J* 18.6 and 10.4 Hz), 5.18 (2H, s), 5.52 (1H, dd, *J* = 10.4 and 6.6 Hz), 7.31 (5H, m); ^{13}C NMR (DMSO) δ 27.3, 34.0, 54.3, 69.2, 84.9, 127.9, 128.4, 128.5, 128.5, 150.1, 152.5, 169.7, 170.8; $[\alpha]_D^{25} = -37.5$ (*c* 1, CH_2Cl_2).

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