Novel access to (3*R*)- and (3*S*)-3-hydroxy-L-aspartic acids, (4*S*)-4-hydroxy-L-glutamic acid, and related amino acids

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Derivatives of L-aspartic and L-glutamic acids can be converted into α-hydroxy acids via oxygenation of the corresponding enolates.

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Des dérivés de l'acide L-aspartique et L-glutamique sont convertis en α-hydroxy acides via des réactions d'oxygénation des énolates correspondants.

There is at present much interest in the asymmetric synthesis of non-proteinogenic as well as unusual amino acids of natural occurrence (for recent excellent monographs, see ref. 1; for selected recent reviews, see ref. 2). In this regard, the β- and γ-hydroxy α-amino acid motif, which can be found in a number of natural products (e.g., cyclosporin (3*a*) and lysobactin (3*b*); see also ref. 4), presents a challenging area for studies in stereocontrolled synthesis. Most of the synthetic routes to β- and γ-hydroxy α-amino acids and their derivatives have been developed only recently and they rely basically on chemical (1, 2), or enzymatic methods (4, 5). In connection with other ongoing projects in our laboratory, we became interested in the synthesis of (3*R*)- and (3*S*)-3-hydroxy-L-aspartic acids. Although the four optical isomers have been obtained by resolution (6) and by individual synthesis (7), recent reports have described alternative methods relying on asymmetric processes using amino acids (8, 9), on utilizing (*R*, *R*)-(+)-tartaric acid as a chiral template (10–16), and on other methodology.

We wish to disclose a novel access to (3*R*)- and (3*S*)-3-hydroxy-L-aspartic acids and (4*S*)-4-hydroxy-L-glutamic acid, as well as to α,γ-dihydroxy amino acids (17), by the stereocontrolled hydroxylation of the dianions derived from appropriate amino acids or their functional equivalents. Although there are ample precedents for the hydroxylation of ester (18),[2] lactone (19), and lactam (20) enolates, there are few practical examples in the amino acid series (21), one, to the best of our knowledge, in the case of acidic amino acids (22), and none with amino lactones. Our choice of L-aspartic and L-glutamic acids as substrates was instigated by the fact that the corresponding β- and γ-hydroxy acids, respectively, are found in nature. In planning our strategy for the stereocontrolled hydroxylation of dianions we wished to control the process by capitalizing on internal asymmetric induction resulting from the inherent chirality and functional disposition of a resident *N*-substituted amino group. We reasoned that by the judicious choice of oxidation reagent, we could alter the stereochemical course of the hydroxylation by taking advantage of the steric bulk in the substrate on the one hand, and chelation of proximal *N*-substituted groups on the other, as illustrated by paths A and B for the enolate resulting from L-aspartic acid in Scheme 1.

To test our plan, we chose the readily available (23) lactone **1** as a model in which the geometry of the dianion is fixed. Thus, lactone **1** was treated with a variety of bases, and the resulting enolate was treated with the Davis oxaziridine reagent (24) on the one hand, and the Mimoun-Vedejs, oxodiperoxymolybdenum pyridine hexamethylphosphoric triamide (MoOPH) reagent (25) on the other (Scheme 2).

As can be appreciated from the results in Table 1, regardless of the nature of the base, hydroxylation with MoOPH led to the preponderance of the *syn* product, albeit in modest yields. The isomeric lactones **2** and **3** were easily separated by chromatography, and variable quantities (up to 20%) of unreacted starting materials were recovered, which is not uncommon with dianions of this type (26). We rationalize the preponderance of this *syn* product by an initial coordination with the carbamate anion (N or O) followed by intramolecular delivery of oxygen as shown in Fig. 1. In view of the initial coordination with MoOPH, the nature of the cation seems to play little or no role in the selectivity.

With the oxaziridine, however, the major product is the *anti* isomer **2**, which most likely results from an approach of the oxidant from a position opposite to the bulky NHCbz group. Moreover, there appears to be an important difference in the ratio of the product **2** and **3**, particularly in the presence of NaHMDS, which gives the highest proportion of the *anti* isomer **2**. The origin of this dependence of selectivity on the nature of the cation is not clear, but could, in part, be due to the states of aggregation of mono and dianions as well as to the reactivity of the intermediate hemiaminal-type species formed with the reagent (18*b*).

Having confirmed the validity of the plan for a reagent and resident functional group-based strategy of hydroxylation with the cyclic model, we investigated the same reactions with *N*-benzyloxycarbonyl-L-asparate **4**. Table 2 summarizes the results in this series, where once again, the combination of the oxaziridine reagent with NaHMDS was found to give the highest selectivity (7:1) in favor of the *erythro* (2*S*,3*R*) isomer **6**.

Acid hydrolysis of **5** and **6**, respectively, gave (3*S*)-3-hydroxy-L-aspartic acid (14) and (3*R*)-4-hydroxy-L-aspartic acid (7), respectively.

With MoOPh, the *threo* isomer (*syn* attack) was favored (Table 2, entries 5–7), but the effect was much less pronounced than in the cyclic model. It is possible that chelation is also taking place in this series although, contrary to the lactone case (Table 1), there seems to be a dependence

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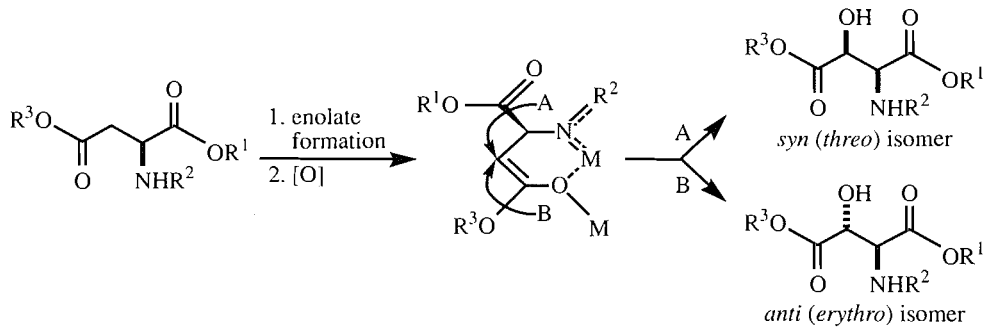
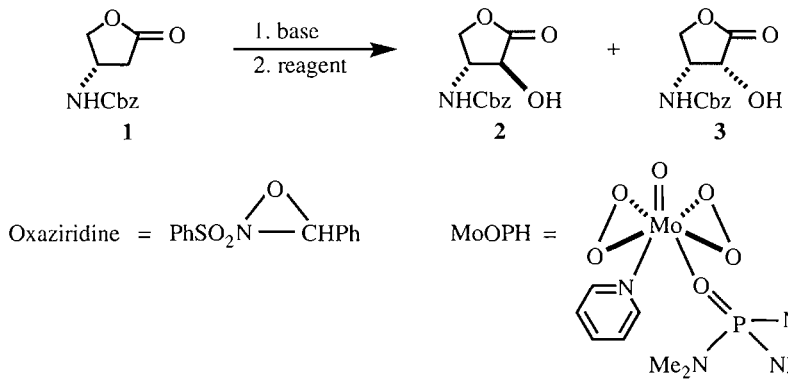
[2]For some examples using molecular oxygen and lead tetracetate, etc., see ref. 18*a*; for the use of 2-sulfonyloxaziridines, see ref. 18*b*; for the use of MoOPH, see ref. 18*c*.



SCHEME 1



SCHEME 2

TABLE 1. Hydroxylation of lactone **1**

	Base	Reagent	Conditions[a] lactone/base/reagent	Yield[b,c] (%)	Ratio[d,e] 2:3
1	LiHMDS	MoOPH	1:4:1.5	30	1:9
2	KHMDS	MoOPH	1:4:1.5	40	1:9
3	NaHMDS	MoOPH	1:4:1.5	36	1:9
4	LiHMDS	Oxaziridine	1:3:1.5	50	4.5:1
5	KHMDS	Oxaziridine	1:3:1.5	70	6.5:1
6	NaHMDS	Oxaziridine	1:3:1.5	56	14:1

[a]THF, −78°C, 6 h (entries 1–3), 1 h (entries 4–6).
[b]Isolated major product.
[c]Varying amounts of starting material were also recovered (10–20%).
[d]Determined by HPLC and by isolation.
[e]Average of three different runs.

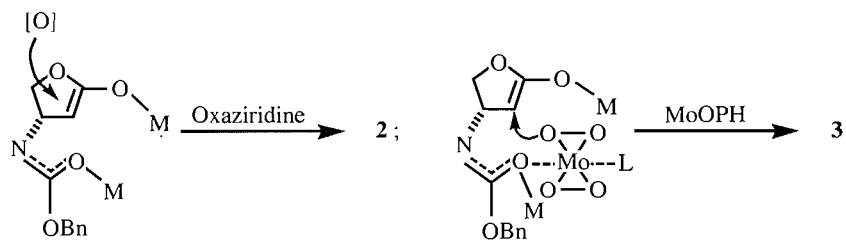


FIG. 1

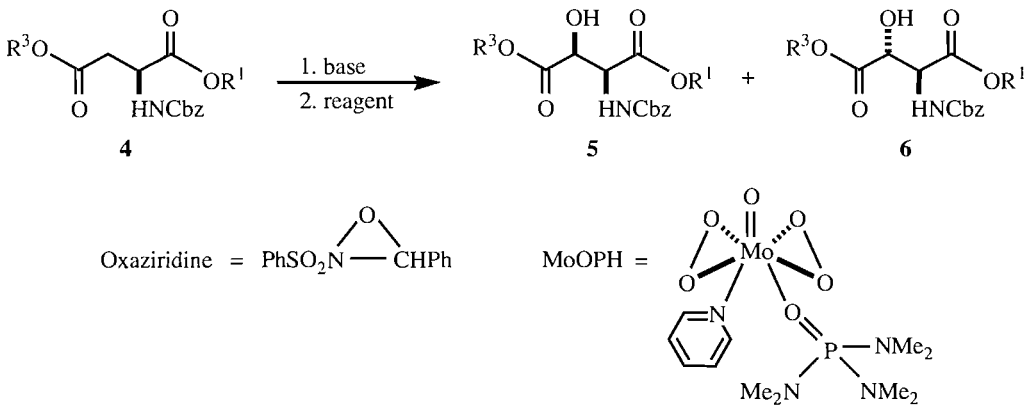
on the nature of the cation. In an effort to clarify the nature of the dianionic species and the influence of the ester group on the selectivity of hydroxylation, we investigated the *N*-tosyl series with different combinations of methyl and *tert*-butyl ester groups (Scheme 4, Table 3).

Thus, localizing the charge on nitrogen (*N*-Ts series) (Scheme 1, R^2 = Ts), in combination with the presence of the bulky α-ester groups, clearly favors the formation of the *erythro* isomer, where a ratio of 45:1 can be obtained (Table 3, entry 5). Interestingly, the bulk of the ester group also has

TABLE 2. Hydroxylation of **4**

	Base	Reagents[a]	Yield (%)[b]	Ratio 6:5[c,d]
1	LDA	Oxaziridine	60	1.5:1
2	LiHMDS	Oxaziridine	60	2.5:1
3	KHMDS	Oxaziridine	70	1.1:1
4	NaHMDS	Oxaziridine	70	7:1
5	LiHMDS	MoOPH	36 (50)	1:2
6	KHMDS	MoOPH	50 (60)	1:1
7	NaHMDS	MoOPH	30 (40)	1:1

[a]THF, −78°C, 15 min (entries 1–4), 4 h (entries 5–7); ester/base/reagent, 1:3:1.5 (entries 1–4), ester/base/reagent, 1:4:2 (entries 5–7).
[b]Yield based on recovered starting material.
[c]Determined by HPLC and by isolation.
[d]Average of three different runs.



SCHEME 3

a synergistic effect in the case of MoOPH, where the selectivity can be increased to 1:4 in favor of the *threo* isomer (Table 3, entry 6), compared to the dimethyl ester series. Evidently in the *N*-Cbz series, selectivity is decreased, possibly due to the larger size of the chelated dianionic species, or due to its different state of aggregation. It should be pointed out that Tamm and co-workers (27) also postulated internal chelation in the hydroxylations with MoOPH.

In view of the limited number of methods for the preparation of enantiomerically pure γ-hydroxy-L-glutamic acid (4, 28–30), it was of interest to extend the hydroxylation reaction to *N*-benzyloxycarbonyl dimethyl L-glutamate **7** (Scheme 5, Table 4). Treatment of the dianion of **7** with MoOPH under a variety of conditions resulted in complete recovery of unchanged starting material, as was recently observed in a related case (21). However, when the oxaziridine was used as oxidant, hydroxylation took place to give the (4*S*)-hydroxy analog as the major (9:1) isomer, when LiHMDS was used as the base. In this series, KHMDS and NaHMDS proved to be much less selective than with **4**. Acid hydrolysis gave (4*S*)-4-hydroxy-L-glutamic acid (28).

The selectivity in this case is intriguing in view of the relative nonproximity of the carbamate to the enolate function. It is possible that the lithium enolate in this case is more conducive to the formation of a π-complex (31) with the aromatic ring of the carbamate, thus imposing an element of conformational constraint, and favoring an approach of the electrophilic reagent that leads to the observed product.

The methodology developed in this work provides an expeditious access to optically pure β- and γ-hydroxylated amino acids in the aspartic and glutamic acid series, respectively. The ability to control the stereochemistry of hydroxylation of dianions of the type reported here, based on the nature of the reagent used, and on the choice of functional group present, should stimulate further development in asymmetric synthesis[3] of related amino acids.

Experimental section

General data

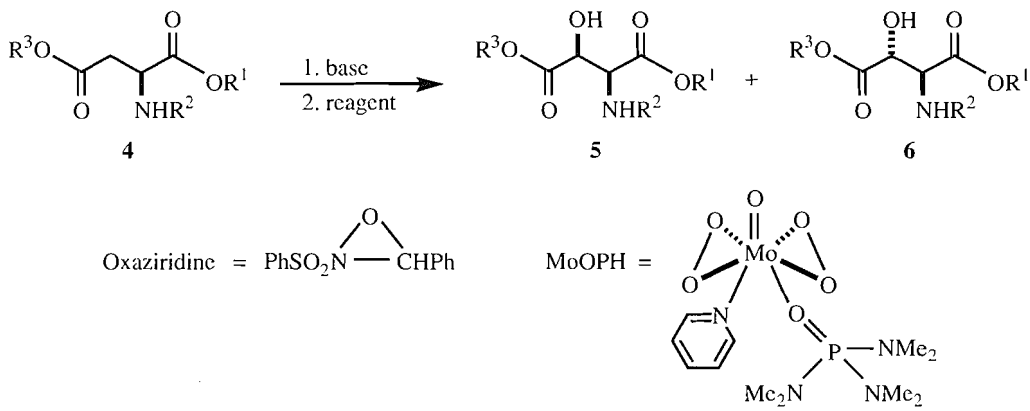
Tetrahydrofuran was distilled over benzophenone and sodium prior to use. Analytical thin-layer chromatography (TLC) was carried out on Merck Kieselgel silica gel 60 F_{254} glass plates. Flash chromatography was performed according to the procedure of Still et al. (33) with Merck silica gel, 230–400 mesh. Infrared (IR) spectra were recorded in chloroform on a Perkin–Elmer 781 spectrometer. The wavenumbers reported are referenced to the polystyrene 1601 cm^{-1} absorption. Nuclear magnetic resonance spectra were obtained on a Bruker WH-400 (^1H 400 MHz) spectrometer with chloroform-*d* as solvent and tetramethylsilane as an internal standard, unless otherwise indicated. ^1H NMR multiplicities are recorded by use of the following abbreviations: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; b, broad; *J*, coupling constant (hertz). High-resolution FAB mass spectra were obtained by means of Kratos MS5OTCTA and AEI-MS 902 spectrometers at the Université de Montréal. Melting points were mea-

[3]The reactivity of dianions resulting from various N-substituted dialkyl aspartates and glutamates depends on the nature of the electrophile, see for example, ref. 32.

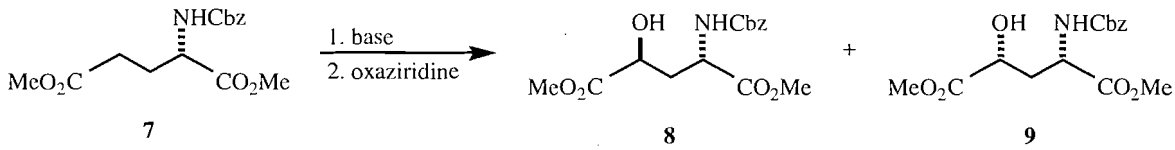
TABLE 3. The effect of different ester and *N*-protective group combinations on the hydroxylation of L-aspartic acid

	Base	Reagent/conditions[a]	R^1	R^2	R^3	Yield[b] (%)	Ratio[d,e] 6:5
1	LiHMDS	Oxaziridine	Me	Cbz	*t*-Bu	40	10:1
2	LiHMDS	Oxaziridine	*t*-Bu	Cbz	Me	60	10:1
3	LiHMDS	Oxaziridine	*t*-Bu	Cbz	*t*-Bu	70	10:1[f]
4	LiHMDS	Oxaziridine	Me	Ts	Me	60	7:1
5	LiHMDS	Oxaziridine	*t*-Bu	Ts	*t*-Bu	57	45:1
6	LiHMDS	MoOPH	*t*-Bu	Cbz	*t*-Bu	40[c]	1:4

[a]THF, −78°C, 5–10 min, ester/base/reagent, 1:3:1.5 (entries 1–5).
[b]Yield of mixture.
[c]Starting material was recovered (20%).
[d]Determined by HPLC and by isolation.
[e]Average of three different runs.
[f]Ratio with KHMDS, 4:1, NaHMDS, 6:1.



SCHEME 4



SCHEME 5

TABLE 4. Hydroxylation of dimethyl *N*-benzyloxycarbonyl-L-glutamate

	Base/conditions[a]	Yield (%)[b,c]	Ratio[d] 8:9
1	LiHMDS	70	9:1
2	KHMDS	70	1:1
3	NaHMDS	56	2.6:1

[a]THF, −78°C, 5–10 min, ester/base/reagent, 1:3:1.5.
[b]Yield of isolated products.
[c]Starting ester was recovered (ca. 10%).
[d]Determined by HPLC.

sured on a Büchi apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 25° C.

Hydroxylation of ***1*** *with 3-phenyl-N-phenylsulfonyloxaziridine*

To a solution of lactone **1** (235 mg, 1 mmol) and 3-phenyl-*N*-phenylsulfonyloxaziridine (392 mg, 1.5 mmol) in THF (5 mL) was added a solution of sodium bis(trimethylsilyl)amide (1 M, 2 mL, 2 mmol) in THF (4 mL) at −78°C. After 15 min, the solution was quenched by addition of camphorsulfonic acid (1.0 g, 4 mmol) in THF (1.0 M), diluted with ethyl acetate, then washed with aqueous solutons of 10% HCl, 5% sodium bicarbonate, and brine. The organic layers were combined, dried ($MgSO_4$), and evaporated to dryness. The crude products were then purified by flash chromatography (ethyl acetate – hexanes, 4:6) to give (2*S*,3*S*)-3-benzyloxycarbonylamino-2-hydroxy-γ-butyrolactone, **2** (140 mg, 56%), and (2*R*,3*S*)-3-benzyloxycarbonylamino-2-hydroxy-γ-butyrolactone, **3** (10 mg, 4%).

For **2**: mp 105–106°C; $[\alpha]_D$ −30 (*c* 1, $CHCl_3$); IR ν_{max} (film): 3600–3200 (OH + NHCbz), 1785 (γ-lactone), 1720–1690 (carbamate) cm^{-1}; ^1H NMR (400 MHz, *O*-acetyl derivative) δ: 2.21 (3H, s, OAc), 3.9 (1H, dd, $J_{4,3}$ = 8.8 Hz, and J_{gem} = 8.8 Hz, H-4a), 4.2–4.16 (1H, m, H-3), 4.34 (1H, d, $J_{2,3}$ = 9.3 Hz, H-2), 4.39 (1H, dd, $J_{4,3}$ = 8.2 Hz, and J_{gem} = 8.8 Hz, H-4b), 5.0 (2H, s, CH_2Ph), 5.5–5.7 (1H, s, *NH*), 7.3–7.40 (5H, s, Ph); MO (O-Acetyl-derivative), *m/z*: 274 (MH^+); $C_{14}H_{15}NO_6$ (273.279).

For **3**: $[\alpha]_D$ +10.75 (*c* 1, $CHCl_3$); IR ν_{max} (film): 3600–3200 (OH + NHCbz), 1785 (γ-lactone), 1740 (ester and carbamate) cm^{-1}; ^1H NMR (400 MHz, O-acetyl derivative) δ: 2.21 (3H, s, OAc), 3.9 (1H, dd, $J_{4,3}$ = 8.8 Hz, and J_{gem} = 8.8 Hz, H-4a), 4.2–

4.16 (1H, m, H-3), 4.34 (1H, d, $J_{2,3}$ = 6.8 Hz, H-2), 4.39 (1H, dd, $J_{4,3}$ = 8.2 Hz, and J_{gem} = 8.8 Hz, H-4b), 5.0 (2H, s, CH_2Ph), 5.5–5.7 (1H, s, *NH*), 7.3–7.40 (5H, s, Ph); MO (O-acetyl derivative), *m/z*: 294 (MH^+); $C_{14}H_{15}NO_6$ (293.279).

Hydroxylation of ***1*** *with MoOPH*

To a solution of lactone **1** (117 mg, 0.5 mmol) in THF at −78°C was added a solution of potassium bis(trimethylsily)amide (0.5 M, 4 mL, 2 mmol) in THF (4 mL) followed by MoOPH (434 mg, 1 mmol). After 15 min, the reaction mixture was quenched by addition of aqueous 10% HCl. The solution was diluted with ethyl acetate, then washed with successively aqueous solutions of 10% HCl, 5% sodium bicarbonate, and brine. The organic layers were combined, dried ($MgSO_4$), and evaporated to dryness. The crude products were then purified by flash chromatography (ethyl acetate – hexanes 4:6) to give **2** (5 mg, 4%) and **3** (45 mg, 65%).

Hydroxylation of ***4*** *with 3-phenyl-*N*-phenylsulfonyloxaziridine*

To a solution of dimethyl *N*-benzyloxycarbonyl-L-asparate **4** (295 mg, 1 mmol) and 3-phenyl-*N*-phenylsulfonyloxaziridine (392 mg, 1.5 mmol) in THF (5 mL) at −78°C was added, dropwise, a solution of sodium bis(trimethylsilyl)amide (1 M, 2.0 mL, 2 mmol) in THF (5 mL). After 15 min, the reaction mixture was quenched by addition of camphorsulfonic acid and processed as described for the synthesis of **2**. The products were then purified by flash chromatography (ethyl acetate – hexanes 4:6) to give (2*S*,3*R*)-dimethyl 3-hydroxy-*N*-benzyloxycarbonyl-L-aspartate **6**, isolated as an oil (190 mg, 61%) and (2*S*,3*S*)-dimethyl 3-hydroxy-*N*-benzyloxycarbonyl-L-aspartate **5**, isolated as an oil (27 mg, 9%).

For **6**: $[\alpha]_D$ +14.58 (*c* 1, $CHCl_3$); IR ν_{max} (film): 3400–3300 (NHCbz), 1750–1730 (esters and carbamate) cm^{-1}; ^1H NMR (300 MHz) δ: 3.34 (1H, d, *J* = 5.3 Hz, OH), 3.78 (3H, s, C(4)OOMe), 3.80 (3H, s, C(1)OOMe), 4.72 (1H, d, $J_{2,3}$ = 3.9 Hz, H-2), 4.75 (1H, d, $J_{3,NH}$ = 9.3 Hz, H-3), 5.10 (2H, s, CH_2Ph), 5.61 (1H, d, $J_{NH,2}$ = 9.3 Hz, NH), 7.34 (5H, s, Ph); MS, *m/z*: 312 (MH^+, 100%); $C_{14}H_{17}NO_7$ (311.294).

For **5**: $[\alpha]_D$ +24.2 (*c* 1, $CHCl_3$); IR ν_{max} (film): 3400–3300 (NHCbz), 1750–1730 (esters and carbamate) cm^{-1}; ^1H NMR (300 MHz) δ: 3.46 (1H, d, *J* = 5.0 Hz, OH), 3.73 (3H, s, C(4)OOMe), 3.83 (3H, s, C(1)OOMe), 4.53 (1H, d, $J_{2,3}$ = 2.0 Hz, H-2), 4.64 (1H , dd, $J_{3,2}$ = 2.2 Hz and $J_{3,NH}$ = 8.4 Hz, H-3), 5.14 (2H, s, CH_2Ph), 5.79 (1H, d, $J_{NH,2}$ = 8.4 Hz, NH), 7.34 (5H, s, Ph); MS, *m/z*: 312 (MH^+, 100%); $C_{14}H_{17}NO_7$ (311.294).

Hydroxylation of ***4*** *with MoOPH*

To a solution of dimethyl *N*-benzyloxycarbonyl-L-aspartate **4** (158 mg, 0.53 mmol) in THF at −78°C was added a solution of potassium bis(trimethylsilyl)amide (0.5 M, 4 mL, 2 mmol) in THF (4 mL) followed by addition of MoOPH (434 mg, 1 mmol). After 15 min, the reaction mixture was quenched by addition of an aqueous solution of 1 N HCl and processed as described above. The crude products were then purified by flash chromatography (ethyl acetate – hexanes 4:6) to give **6** (27 mg, 16%) and **5** (55 mg, 34%), isolated as oils.

*Hydroxylation of di-*tert*-butyl-*N*-p-tolylsulfonyl-*L*-aspartate with 3-phenyl-*N*-phenylsulfonyl oxaziridine*

To a solution of di-*tert*-butyl-*N*-*p*-tolylsulfonyl-L-aspartate (104 mg, 0.27 mmol) at −78°C was added, dropwise, a solution of lithium hexamethyldisilazane (0.78 mmol) in THF (5 mL). After 2 h, 3-phenyl-*N*-phenylsulfonyl oxaziridine (102 mg, 0.39 mmol) in THF (2 mL) was added. The reaction was quenched, after 15 min, by addition of camphorsulfonic acid (0.26 g, 1.1 mmol) in THF (1.0 M). The solution was diluted with ethyl acetate and processed as described above. The crude products were purified by flash chromatography (ethyl acetate – hexanes 1:1) to give (2*S*-3*R*)-di-*tert*-butyl-3-hydroxy-*N*-tosyl-L-aspartate and (2*S*,3*S*)-di-*tert*-butyl-3-hydroxy-*N*-tosyl-L-aspartate as a 45:1 (*anti*:*syn*) mixture of diastereomers (62 mg, 57%); IR ν_{max} (film): 3400–2900 (OH + NHCbz), 1750–1730 (esters) cm^{-1}; ^1H NMR (300 MHz) δ: 1.23 (9H, s, *tert*-butyl), 1.57 (9H, s, *tert*-butyl), 2.40 (3H, s, CH_3), 3.02 (1H, m, OH-3), 4.275 (1H, dd, $J_{2,OH}$ = 10.8 Hz and $J_{2,3}$ = 2.26 Hz, H-2), 4.39–4.42 (1H, M, H-3), 5.3 (1H, d, $J_{NH,2}$ = 10.8 Hz, NH), 7.29 (2H, d, *J* = 8 Hz, Ph), 7.75 (2H, d, *J* = 6.5 Hz, Ph).

*Hydroxylation of di-*tert*-butyl-*N*-benzyloxycarbonyl-*L*-aspartate with MoOPH*

To a solution of di-*tert*-butyl-*N*-benzyloxycarbonyl-L-aspartate (100 mg, 0.264 mmol) in THF (10 mL) at −78°C was added a solution of lithium bis(trimethylsilyl)amide (2.1 mmol) in THF (4 mL). After 2 h, MoOPH (229 mg, 0.527 mmol) was added as a solid in one portion at −78°C. After 4 h, the solution was quenched by addition of an aqueous solution of 1 N HCl, then processed as described above. The crude products were purified by flash chromatography (ethyl acetate – hexanes 2:8) to give 42 mg, 40%) of (2*S*,3*R*)-di-*tert*-butyl-3-hydroxy-*N*-benzyloxycarbonyl-L-aspartate and (2*S*,3*S*)-di-*tert*-butyl-3-hydroxy-*N*-benzyloxycarbonyl-L-aspartate isolated as a 1:4 (*anti*:*syn*) mixture of diastereomers; IR ν_{max} (film): 3600–3300 (OH + NHCbz), 1730 (esters) cm^{-1}; ^1H NMR (300 MHz, for the OAc derivative) δ: 1.469 (9H, s, *tert*-butyl), 1.496 (9H, s, *tert*-butyl), 2.109 (3H, s, OAc), 4.852 (1H, dd, $J_{2,NH}$ = 8,1 Hz and $J_{2,3}$ = 3.2 Hz, H-2), 5.125 (2H, s, CH_2Ph), 5.355 (1H, d, $J_{2,3}$ = 3.2 Hz, H-3), 5.585 (1H, d, $J_{NH,2}$ = 8.1 Hz, NH), 7.36 (5H, s, Ph); MS, *m/z*: 278 (50%) 222 (55%), 89 (95%); HRMS, calcd. for $C_{20}H_{29}NO_7$: 395.1944; found: 395.4520.

Hydroxylation of dimethyl N*-benzyloxycarbonyl-*L*-glutamate (7) with 3-phenyl-*N*-phenylsulfonyl oxaziridine*

To a solution of dimethyl *N*-benzyloxycarbonyl-L-glutamate (120 mg, 0.408 mmol) and 3-phenyl-*N*-phenylsulfonyl oxaziridine (160 mg, 0.612 mmol) in THF (5 mL) at −78°C (acetone – Dry Ice) was added, dropwise, a solution of lithium bis(trimethylsilyl)amide (1 M, 1.22 mL, 1.22 mmol) in THF (5 mL). After 15 min, the solution was quenched by addition of camphorsulfonic acid (0.408 g, 1.8 mmol) in THF (1.0 M). The solution was diluted with ethyl acetate, washed with an aqueous solution of 10% HCl, then processed as described above. The crude products were purified by flash chromatography (ethyl acetate – hexanes 1:1) to give (92 mg, 70%) of (2*S*,4*S*)-dimethyl 4-hydroxy-*N*-benzyloxycarbonyl-L-glutamate as a 9:1 mixture of inseparable diastereomers; $[\alpha]_D$ +9.0 (*c* 1, $CHCl_3$); IR ν_{max} (film): 3600–3200 (NHCbz + OH), 1760–1690 (esters and carbamate) cm^{-1}; ^1H NMR (300 MHz) δ: 2.2 (2H, m, H-3a and H-3b), 3.5 (1H, d, *J* = 4.4 Hz, OH), 3.73 (3H, s, COOMe), 3.75 (3H, s, COOMe), 4.25 (1H, m, H-2), 4.64 (1H, m, H-4), 5.11 (2H, s, CH_2Ph), 5.8 (1H, d, $J_{NH,4}$ = 7.8 Hz, NH), 7.34 (5H, s, Ph); MS, *m/z*: 326 (30%, MH^+), 282 (100%, $-CO_2$); HRMS, calcd. for $C_{15}H_{19}NO_7$: 325.1161; found: 325.1120.

*(3*R*)-3-Hydroxy-*L*-aspartic acid*

A solution of **6** (100 mg, 0.321 mmol), in 6 N HCl, was heated at reflux for 1.5 h. The solution was cooled, diluted with EtOAc, processed in the usual way, and the aqueous layer was evaporated to a volume of 2 mL. Acetone was then added and the resulting crystals were isolated by filtration to give the title compound as a white crystalline solid (33 mg, 69%); mp >200°C, $[\alpha]_D$ +45.6 (*c* 0.5, HCl 1 N) (lit. (16) mp >220°C, $[\alpha]_D$ +49 (*c* 2.85, HCl 1 N)).

*(3*S*)-3-Hydroxy-*L*-aspartic acid*

A solution of **5** (100 mg, 0.321 mmol), in 6 N HCl, was heated at reflux for 1.5 h. The solution was processed as described above to give the title compound as a white crystalline solid (33 mg, 69%); mp >200°C, $[\alpha]_D$ +1 (*c* 2, HCl 1 N) (lit. (7) mp >200°C, $[\alpha]_D$ +1.3 (*c* 2, HCl 1 N)).

*(4*S*)-4-Hydroxy-*L*-glutamic acid*

A solution of **8** (100 mg, 0.308 mmol), in 6 N HCl, was heated at reflux for 1.5 h. The solution was cooled, then processed as described above to give the title compound as a white crystalline solid (35 mg, 69%); mp >200°C, $[\alpha]_D$ +55 (*c* 1, HCl 5 N) (lit. (28) mp >200°C, $[\alpha]_D$ +61 (*c* 1, HCl 5 N)).

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