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Chemoselectivity in the Reduction of (2*S*,4*S*)-4-Amino-5-oxoproline Derivatives with Borane Complexes

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Reduction of the carbonyl groups in *N*-protected (2*S*,4*S*)-4-amino-5-oxo-1-phenylprolinates with BH_3 complexes resulted in (2*S*,4S)-4-aminoproline or (2*S*,4*S*)-4-aminoprolinol derivatives depending on the reaction conditions and the type of protecting groups used.

Introduction

Optically active prolines including 4-aminoproline derivatives have been widely used in organic synthesis as chiral synthons,[1] fragments of conformationally constrained peptides,[2] substrates of glutamate neuroreceptors,[3] and the components of catalysts for asymmetric synthesis.[4] One of the efficient synthetic approaches for producing various substituted prolines involves the reduction of the lactam carbonyl in the appropriate 5-oxoproline derivatives. BH_3 complexes have been used for selective reduction of *N*-Boc protected 5-oxoprolinates.[5]

In the present work we explored the reduction of various *N*- and *C*-protected derivatives of (2*S*,4*S*)-4-amino-5-oxo-1-phenylproline[6] (**1**) with BH_3 complexes (Figure 1). 5-Oxo-1-phenylprolines were chosen as the substrates for our study because their reduction results in chiral 1-phenylprolines and 1-phenylprolinols. It should be noted that 1-arylprolines are of special interest for preparing catalysts for asymmetric synthesis,[7] and they are also promising biologically active compounds.[8] The probable reduction mechanism involves the coordination of the borane with the carbonyl oxygen atom.[9] Accordingly, we consider that the number and type of protecting groups used can influence the spatial accessibility and the reactivity of the different carbonyl groups to thereby influence the chemoselectivity of the reduction of the lactam and ester groups.

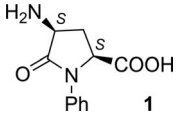

Figure 1. (2*S*,4*S*)-4-Amino-5-oxo-1-phenylproline.

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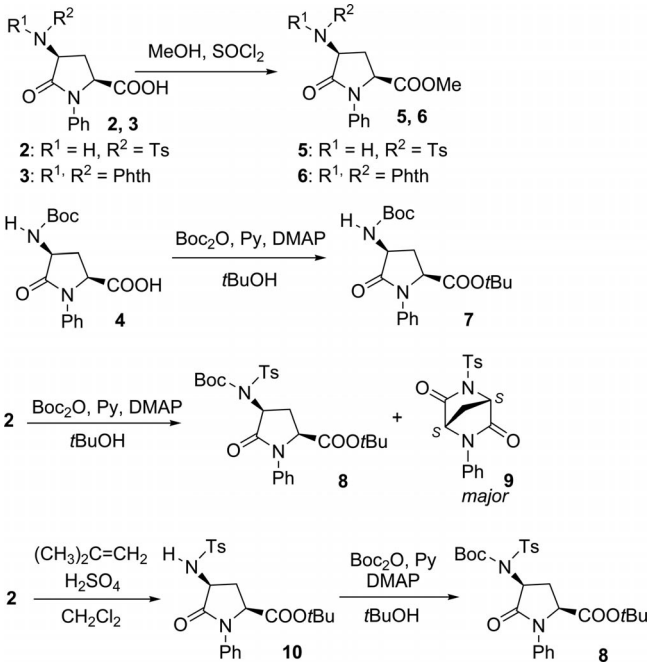
Results and Discussion

N-Protected derivatives of 4-amino-5-oxo-1-phenylproline (**1**), such as 4-tosylamino- (**2**), 4-phthalimido- (**3**), and 4-Boc-amino- (**4**) (2*S*,4*S*)-5-oxo-1-phenylprolines were prepared as described previously.[6]

Methyl esters **5** and **6** were prepared in high yields according to the standard procedure of treating *N*-tosylated **2** and *N*-phthaloyl-protected **3** with MeOH and thionyl chloride, respectively (Scheme 1). *tert*-Butyl ester **7** was obtained by the action of Boc_2O/DMAP on *N*-Boc derivative **4** in *t*BuOH. When we used Boc_2O in *t*BuOH for esterification of compound **2**, we obtained the *tert*-butyl ester of *N*-dipro-



Scheme 1. Synthesis of alkyl esters of *N*-protected 4-amino-5-oxo-1-phenylprolines.

tected 4-amino-5-oxo-1-phenylproline (**8**) in a low yield due to the formation of the byproduct 4-tosyl-5-phenyl-2,5-diazabicyclo[2.2.1]heptan-3,6-dione (**9**) obtained by intermolecular cyclization as described previously.[6] Thus, we first prepared *tert*-butyl ester **10** by esterification of *N*-tosyl derivative **2** with 2-methylpropene[10] in dichloromethane in the presence of sulfuric acid. We then introduced *N*-Boc protection using Boc_2O/DMAP in *t*BuOH to obtain compound **8** in 81% overall yield. The structure of compound **8** was confirmed by X-ray crystallographic analysis (Figure 2).

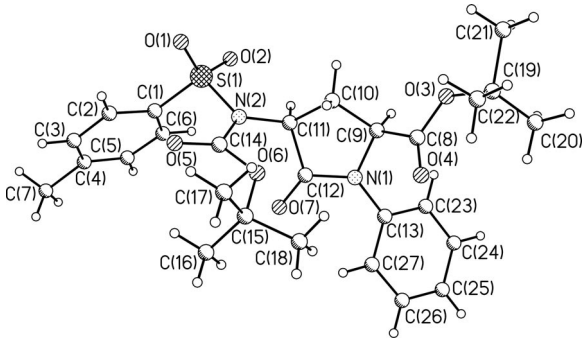


Figure 2. X-ray crystal structure of compound **8**.

Reduction of compounds **5**–**8** and **10** was carried out using borane complexes, such as BH_3·Me_2S and BH_3·THF in THF under an atmosphere of argon at various temperatures (Scheme 2). We used different amounts of reducing agent, from 1.5 to 4 equiv. relative to the substrate. The duration of the reduction was varied from 3 to 35 d.

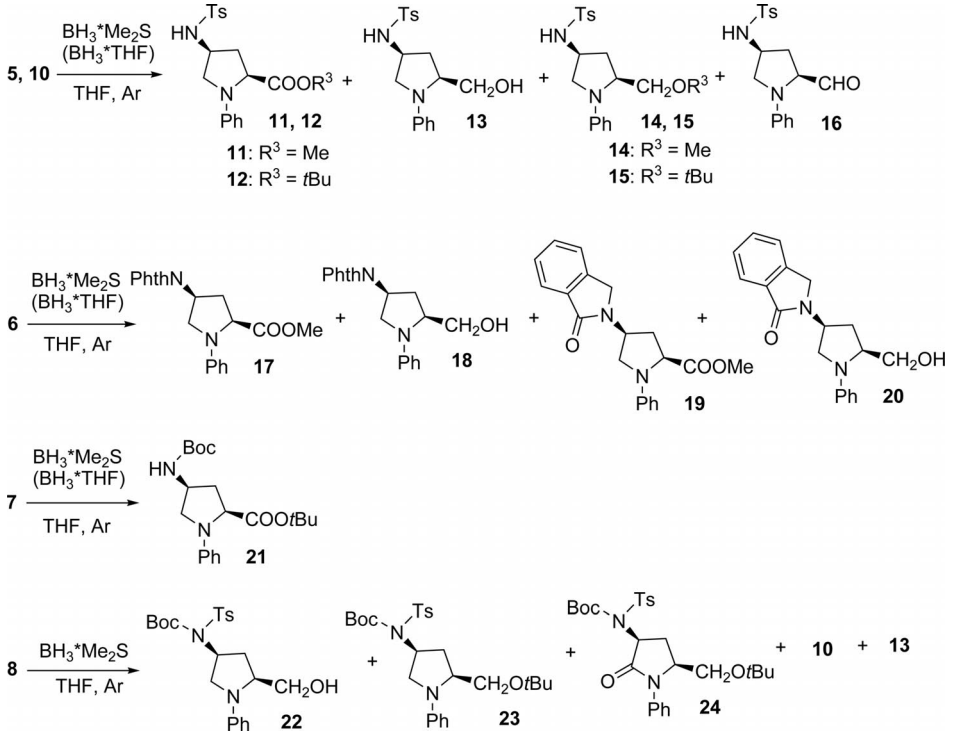
Each reaction was quenched by addition of MeOH. After evaporation to dryness under reduced pressure each residue was separated by flash column chromatography on silica gel, and the major reaction products were isolated. The structures of the isolated compounds were confirmed by ^1H and ^{13}C NMR spectroscopy, elemental analysis, and LC–MS data.

The composition of the mixtures of the reaction products was quantitatively estimated based on isolated yields (Table 1). When we failed to separate the reaction products we applied ^1H NMR spectroscopy and HPLC data.

It was found that reaction of *N*-tosyl compounds **5** and **10** with 4 equiv. of BH_3 complex led to reduction of not only the lactam carbonyl groups affording esters **11** and **12** but also the ester carbonyl groups affording ethers **14** and **15**, prolinol **13**, and aldehyde **16** (Scheme 2). Decreasing the amount of reducing agent did not result in a considerable increase in the chemoselectivity, but diminished the conversion of the starting compounds.

In the case of the reduction of compound **5**, conducting the reaction at low temperature (–5 °C) made it possible to increase the yield of ester **11** to 44% (Table 1, Entry 2), whereas when the reaction was carried out at 40 °C the major product of reduction with BH_3·Me_2S was prolinol **13** (Table 1, Entry 9; 72% yield). The structure of compound **13** was established on the basis of X-ray crystallographic data (Figure 3).

In the case of *tert*-butyl ester **10**, together with the lactam carbonyl, the ester carbonyl group also underwent significant reduction. Thus, when the reduction was carried out at –5 °C for 12 d the major reduction products included not



Scheme 2. Reduction of compounds **5**–**8** and **10**.

Table 1. Reaction conditions and the results of reduction of compounds **5**–**8** and **10**.

Entry	Reaction conditions						Reduction products					
	Substrate	Temp. [°C]	Borane (equiv.)	Time [d]	Ester	Yield[a] [%]	Prolinol	Yield[a] [%]	Ether	Yield[a] [%]	Other products	Yield[a] [%]
1	**5**	–5	BH_3·Me_2S (2)	3	**11**	38	**13**	8			**16**	3
2	**5**	–5	BH_3·Me_2S (4)	3	**11**	44	**13**	22			**16**	4
3	**5**	–5	BH_3·Me_2S (4)	12	**11**	20	**13**	59			**16**	5
4	**5**	–5	BH_3·Me_2S (4)	35	**11**	7	**13**	70	**14**	2	**16**	8
5	**5**	+25	BH_3·Me_2S (2)	7	**11**	4	**13**	63				
6	**5**	+25	BH_3·Me_2S (4)	7			**13**	72	**14**	2	**16**	3
7	**5**	+25	BH_3·THF (1.5)	5	**11**	21						
8	**5**	+25	BH_3·THF (4)	8			**13**	52	**14**	12		
9	**5**	+40	BH_3·Me_2S (4)	7			**13**	72	**14**	4		
10	**5**	+40	BH_3·THF (4)	7			**13**	55	**14**	20		
11	**10**	–5	BH_3·Me_2S (4)	3	**12**	43	**13**	9			**16**	11
12	**10**	–5	BH_3·Me_2S (4)	7	**12**	48	**13**	12	**15**	2	**16**	14
13	**10**	–5	BH_3·Me_2S (4)	12	**12**	42	**13**	14	**15**	3	**16**	20
14	**10**	–5	BH_3·Me_2S (4)	35	**12**	21	**13**	23	**15**	8	**16**	25
15	**10**	+25	BH_3·Me_2S (4)	7			**13**	37	**15**	38	**16**	12
16	**6**	–5	BH_3·Me_2S (4)	35	**17**	24	**18**[b]	11			**19**	22
17	**6**	+25	BH_3·THF (1.5)	7	**17**	21	**18**[b]	20				
18	**6**	+25	BH_3·Me_2S (4)	7	**17**	26	**18**[b]	10			**19**	28
											20	11
19	**7**	–5	BH_3·Me_2S (4)	35	**21**	77						
20	**7**	+25	BH_3·Me_2S (4)	7	**21**	43						
21	**8**	+25	BH_3·Me_2S (4)	35					**23**	11	**24**[b]	18
											10	2
22	**8**	+40	BH_3·Me_2S (4)	22			**22**[b]	12	**23**	48	**13**	14

[a] Isolated yield. [b] Compounds **18**, **22**, and **24** were not isolated in pure form; yields were determined on the basis of ^{1}H NMR spectroscopy.

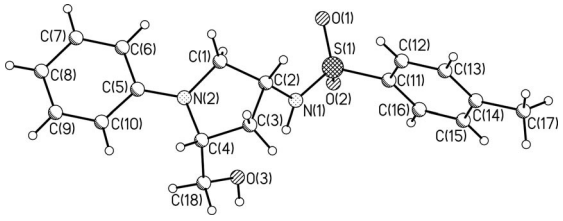


Figure 3. X-ray crystal structure of compound **13**.

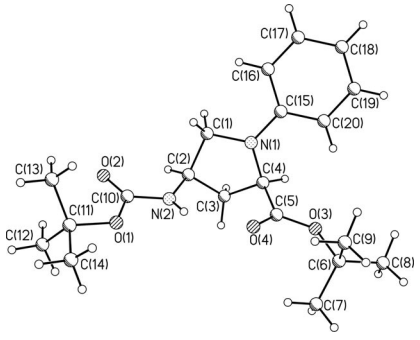


Figure 4. X-ray crystal structure of compound **21**.

only ester **12** (42% yield), but prolinol **13** (14% yield) and aldehyde **16** (20% yield) (Table 1, Entry 13) as well.

Treatment of *N*-phthaloyl derivative **6** with borane complexes resulted not only in the reduction of the lactam and ester carbonyl groups affording ester **17** and prolinol **18** but also in the partial reduction of the phthalimido group affording compounds **19** and **20**. The amount of **19** and **20** produced decreased when the reaction temperature was lowered, as did the conversion of starting compound **6** (Table 1, Entries 16–18). The yield of prolinol **18**, the product of reduction of the ester carbonyl in *N*-phthaloyl compound **6**, was lower than the yield of prolinol **13**, the product of *N*-tosyl-protected **5** (Table 1 Entries 3–8 and 16–18).

The only isolated reduction product for *N*-Boc derivative **7** with BH_3·Me_2S was ester **21**, whose structure was confirmed by X-ray crystallographic data (Figure 4). When reductions was carried out at –5 °C for 35 d or at +25 °C for 7 d the yield of compound **21** was 77 or 43%, respectively (Table 1, Entries 19 and 20).

The reduction of sterically constrained compound **8** with both *N*-Boc and *N*-tosyl groups at the same nitrogen atom proceeded more slowly. When the reaction was carried out with BH_3·Me_2S at +25 °C for 35 d the conversion was 46% and the composition of reduction products was distinctive (Scheme 2). The product mixtures at both +40 and +25 °C contained alcohol **22**, whose structure was assigned on the basis of ^{1}H NMR spectroscopy and LC–MS data, ether **23** with the lactam carbonyl reduced, and ether **24**, in which the lactam carbonyl was untouched. The relative configuration of *cis*-**23** was confirmed by X-ray crystallographic data (Figure 5) and a 2D NOESY spectrum, in which cross-peaks between 3-H^A and both 2-H and 4-H were observed. Compounds **10** and **13** without the *N*-Boc group were also detected among the reaction products. Thus, an increase in the steric hindrance caused by the presence of both *N*-tosyl

and *N*-Boc protecting groups at C-4 led to an increase in the number of the reduction products.

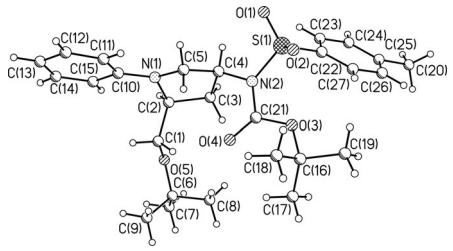


Figure 5. X-ray crystal structure of compound **23**.

Thus, it has been found that the chemoselectivity of reduction of *N*-protected (2*S*,4*S*)-4-amino-5-oxo-1-phenylprolinates is determined to a large degree by the nature of the protecting groups, and to a smaller degree on the type of borane complex and the reagent ratios used (Table 1).

Conclusions

In sum, it has been shown that, depending on the reaction conditions and the type of protecting groups attached to the substrate, one can obtain both (2*S*,4*S*)-4-aminoproline and (2*S*,4*S*)-4-aminoprolinol derivatives as a result of the borane-mediated reduction of the carbonyl moieties in *N*-protected (2*S*,4*S*)-4-amino-5-oxo-1-phenylprolinates. In particular, we obtained certain (2*S*,4*S*)-4-amino-1-phenylproline and (2*S*,4*S*)-4-amino-1-phenylprolinol derivatives in approximately 70% yields.

Experimental Section

General: (2*S*,4*S*)-4-[(4-Methylbenzenesulfonyl)amino]-5-oxo-1-phenylproline (**2**), (2*S*,4*S*)-5-oxo-1-phenyl-4-phthalimidoproline (**3**), and (2*S*,4*S*)-4-(*tert*-butyloxycarbonyl)amino-5-oxo-1-phenylproline (**4**) were prepared as described previously.[6] 2-Methylpropene was obtained according to a literature procedure[10] and was used as such in the subsequent step. All other reagents were of commercial quality. Solvents were dried and purified by standard methods. Routine monitoring of reaction mixtures was carried out by using Sorbfil UV 254 (Russia) TLC aluminum-plated silica gel. Silica gel 60 (230–400 mesh) was used for flash chromatography. Analytical HPLC was performed with a LiChrosorb Si-60 (4 × 250 mm, 5 μm) column, with a flow rate of 1 mL/min, and by using a tuneable UV detector set at 230 nm. Mixtures of hexane (solvent A) and *i*PrOH (solvent B) were used as the mobile phases. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using TMS as a reference. The assignment of chemical ^{1}H and ^{13}C shifts for compounds **11**, **13**, and **23** was based on standard 2D NMR techniques (COSY, ^{1}H–^{1}H NOESY, ^{1}H–^{13}C HSQC, and HMBC). Optical rotation values were measured with a Perkin–Elmer M 341 polarimeter. All optical rotations were obtained at room temperature. LC–MS data were collected by LCMS solution software with a LCMS-2010 instrument (Shimadzu) operating in positive and negative ion mode with ESI or APCI probe installed at N_2 flow rate of 4.5 or 2.5 L/min, correspondingly. The probe voltage was set to 4.5 kV, and the APCI probe temperature was set to 400 °C. The curved desolvation line (CDL) and block heater were set at 250 and 200 °C, respectively. Quadrupole array (Q-array) and CDL were used in scan mode according to the autotuning parameters. LC separation was performed using ODS columns made by Phenomenex [Luna C18(2), 150 × 2.0 mm, 3 μm] or Supelco (Supelcosil LC-18 250 × 4.6 mm, 5 μm) at 60 °C. MeCN/H_2O or MeOH/H_2O mixtures were used as solvents.

Methyl (2*S*,4*S*)-4-(4-Methylbenzenesulfonyl)amino-5-oxo-1-phenylprolinate (5): $SOCl_2$ (0.50 mL, 6.88 mmol) was added dropwise to a stirred solution of compound **2** (1.00 g, 2.67 mmol) in dry MeOH (20 mL) at –5 °C. The reaction mixture was kept for 0.5 h at that temperature and for 1 d at r.t. and then evaporated to dryness under reduced pressure. The residue was recrystallized from benzene and dried at 80 °C in vacuo to give compound **5** (0.920 g, 89%) as a white solid. M.p. 190–193 °C. $[\alpha]_D$ = –2.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.22 (ddd, *J* = 13.1, 8.8, 8.0 Hz, 1 H, 3-H^B), 2.42 (s, 3 H, Me-Ts), 2.98 (ddd, *J* = 13.1, 8.6, 7.2 Hz, 1 H, 3-H^A), 3.67 (s, 3 H, OMe), 3.94 (td, *J* = 8.6, 3.9 Hz, 1 H, 4-H), 4.71 (dd, *J* = 8.0, 7.2 Hz, 1 H, 2-H), 5.47 (d, *J* = 3.9 Hz, 1 H, NH), 7.20 (m, 1 H, H*p*-Ph), 7.31–7.37 (m, 6 H, Ph, Ts), 7.81 (m, 2 H, Ts) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.53 (Me-Ts), 32.22 (C-3), 52.93, 53.74 (OMe, C-4), 58.58 (C-2), 121.71 (C*o*-Ph), 126.43 (C*p*-Ph), 127.36 (C*o*-Ts), 129.11 and 129.86 (C*m*-Ts, C*m*-Ph), 135.89 and 137.00 (C*i*-Ph, C*i*-Ts), 144.02 (C*p*-Ts), 169.78 and 170.84 (C-5, *C*O_2Me) ppm. $C_{19}H_{20}N_2O_5S$ (388.44): calcd. C 58.75, H 5.19, N 7.21, S 8.26; found C 58.79, H 5.14, N 7.10, S 8.18. HPLC (A/B, 40:1): t_R = 21.2 min.

Methyl (2*S*,4*S*)-5-Oxo-1-phenyl-4-phthalimidoprolinate (6): $SOCl_2$ (0.25 mL, 3.4 mmol) was added dropwise to a stirred suspension of compound **3** (0.500 g, 1.43 mmol) in dry MeOH (10 mL) at 0 °C. The reaction mixture was kept for 0.5 h at that temperature and for 1 d at r.t. and then evaporated to dryness under reduced pressure. The residue was recrystallized from MeOH to give compound **6** (0.50 g, 96%) as white crystals. M.p. 175–177 °C. $[\alpha]_D$ = +30.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.65 (ddd, *J* = 12.5, 10.5, 8.9 Hz, 1 H, 3-H^B), 2.93 (ddd, *J* = 12.5, 9.5, 7.6 Hz, 1 H, 3-H^A), 3.67 (s, 3 H, OMe), 4.92 (dd, *J* = 8.9, 7.6 Hz, 1 H, 2-H), 5.14 (dd, *J* = 10.5, 9.5 Hz, 1 H, 4-H), 7.22 (m, 1 H, H*p*-Ph), 7.39 (m, 2 H, H*m*-Ph), 7.48 (m, 2 H, H*o*-Ph), 7.75 (m, 2 H, Phth), 7.88 (m, 2 H, Phth) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.54 (C-3), 49.49 (C-4), 52.73 (OMe), 57.94 (C-2), 122.24 (C*o*-Ph), 123.62 (C*o*-Phth), 126.19 (C*p*-Ph), 128.96 (C*m*-Ph), 131.82 (C*m*-Phth), 134.32 (C*i*-Phth), 137.61 (C*i*-Ph), 167.20 (*C*O-Phth), 168.29 (C-5), 170.32 (*C*O_2Me) ppm. $C_{20}H_{16}N_2O_5$ (364.36): calcd. C 65.93, H 4.43, N 7.69; found C 65.84, H 4.31, N 7.52. HPLC (A/B, 20:1): t_R = 26.4 min.

***tert*-Butyl (2*S*,4*S*)-4-(*tert*-Butyloxycarbonyl)amino-5-oxo-1-phenylprolinate (7):** Py (0.25 mL, 3.11 mmol), DMAP (0.038 g, 0.31 mmol) and Boc_2O (1.06 g, 4.83 mmol) were added to a stirred suspension of compound **4** (1.00 g, 3.12 mmol) in *t*BuOH (25 mL). The reaction mixture was stirred for 12 h at r.t., poured into cooled water (125 mL), and kept for 0.5 h at 10 °C. Filtration of the precipitate gave compound **7** (1.02 g, 87%) as colorless crystals. M.p. 171.5–172.5 °C (subl.) $[\alpha]_D$ = –14.9 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.25 (s, 9 H, *t*Bu), 1.41 (s, 9 H, *t*Bu), 1.89 (ddd, *J* = 11.5, 11.0, 9.6 Hz, 1 H, 3-H^B), 2.68 (ddd, *J* = 11.5, 8.8, 7.0 Hz, 1 H, 3-H^A), 4.42 (ddd, *J* = 11.0, 8.9, 8.8 Hz, 1 H, 4-H), 4.81 (dd, *J* = 9.6, 7.0 Hz, 1 H, 2-H), 7.17 (m, 1 H, H*p*-Ph), 7.34 (d, *J* = 8.9 Hz, 1 H, NH), 7.36–7.40 (m, 4 H, Ph) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 27.25 and 28.15 (both Me-*t*Bu), 29.43 (C-3), 51.20 (C-4), 57.31 (C-2), 78.16 and 81.42 (both C-*t*Bu), 121.36 (C*o*-Ph), 124.95 (C*p*-Ph), 128.44 (C*m*-Ph), 138.47 (C*i*-Ph), 155.29 (N*C*O_2-*t*Bu), 169.65 and 171.46 (*C*O_2-*t*Bu, C-5) ppm. $C_{20}H_{28}N_2O_5$ (376.45): calcd. C 63.81, H 7.50, N 7.44; found C 63.52, H 7.60, N 7.35. HPLC (A/B, 40:1): t_R = 14.0 min.

***tert*-Butyl (2*S*,4*S*)-4-(4-Methylbenzenesulfonyl)amino-5-oxo-1-phenylprolinate (10):** Concentrated H_2SO_4 (0.1 mL) was added to a stirred suspension of compound **2** (0.75 g, 2.0 mmol) in dry CH_2Cl_2 (6.5 mL). The reaction mixture was cooled to –18 °C. Freshly prepared 2-methylpropene was bubbled into the reaction mixture. The reaction bottle was tightly sealed, and the reaction mixture was stirred for 1 d until the solution clarified. The reaction mixture was then poured into a 1:1 mixture of EtOAc and 5% aqueous Na_2CO_3 (140 mL). The organic layer was separated, washed with aqueous Na_2CO_3 (5%) and brine to neutral pH, dried with Na_2SO_4, and then evaporated to dryness under reduced pressure. The residue was reprecipitated from EtOAc solution with hexane to give compound **10** (0.76 g, 88%) as colorless crystals. M.p. 179–183 °C (decomp.). $[\alpha]_D$ = +1.4 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (s, 9 H, *t*Bu), 2.19 (ddd, *J* = 13.0, 9.0, 8.3 Hz, 1 H, 3-H^B), 2.41 (s, 3 H, Me-Ts), 2.97 (ddd, *J* = 13.0, 8.3, 7.0 Hz, 1 H, 3-H^A), 3.89 (ddd, *J* = 9.0, 8.3, 3.8 Hz, 1 H, 4-H), 4.57 (dd, *J* = 8.3, 7.0 Hz, 1 H, 2-H), 5.45 (d, *J* = 3.8 Hz, 1 H, NH), 7.19 (m, 1 H, H*p*-Ph), 7.30–7.38 (m, 6 H, Ph, Ts), 7.82 (m, 2 H, Ts) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.52 (Me-Ts), 27.57 (Me-*t*Bu), 32.32 (C-3), 53.85 (C-4), 59.59 (C-2), 83.22 (C-*t*Bu), 121.69 (C*o*-Ph), 126.19 (C*p*-Ph), 127.38 (C*o*-Ts), 128.92 (C*m*-Ph), 129.86 (C*m*-Ts), 135.82 and 137.25 (C*i*-Ts, C*i*-Ph), 143.99 (C*p*-Ts), 169.19 and 169.64 (C-5, *C*O$_2$-*t*Bu) ppm. $C_{22}H_{26}N_2O_5S$ (430.52): calcd. C 61.38, H 6.09, N 6.51, S 7.45; found C 60.97, H 5.97, N 6.19, S 7.51. HPLC (A/B, 40:1): t_R = 8.9 min.

***tert*-Butyl (2*S*,4*S*)-4-[(*tert*-Butyloxycarbonyl)(4-methylbenzenesulfonyl)amino]-5-oxo-1-phenylprolinate (8):** Py (0.12 mL, 1.49 mmol), DMAP (10 mg, 0.08 mmol), and Boc_2O (300 mg, 1.38 mmol) were added to a stirred solution of compound **10** (352 mg, 0.82 mmol) in *t*BuOH (9 mL). The reaction mixture was stirred for 18 h at r.t., poured into water (40 mL), and kept for 2 h at 0 °C. Filtration of the precipitate gave compound **8** (398 mg, 92%) as colorless crystals. M.p. 166–172 °C (decomp.). $[\alpha]_D$ = –45.4 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 9 H, *t*Bu), 1.37 (s, 9 H, *t*Bu), 2.42 (s, 3 H, Me-Ts), 2.63 (ddd, *J* = 11.8, 11.0, 9.6 Hz, 1 H, 3-H^B), 2.95 (ddd, *J* = 11.8, 9.0, 7.4 Hz, 1 H, 3-H^A), 4.70 (dd, *J* = 9.6, 7.4 Hz, 1 H, 2-H), 5.33 (dd, *J* = 11.0, 9.0 Hz, 1 H, 4-H), 7.19 (m, 1 H, H*p*-Ph), 7.31 (m, 2 H, H*o*-Ph), 7.35–7.43 (m, 4 H, H*m*-Ph, Ts), 8.02 (d, *J* = 8.1 Hz, 2 H, Ts) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.63 (Me-Ts), 27.62 and 27.95 (both Me-*t*Bu), 28.95 (C-3), 57.28 and 58.05 (C-4, C-2), 82.59 and 85.45 (both C-*t*Bu), 121.87 (C*o*-Ph), 125.76 (C*p*-Ph), 128.16 (C*o*-Ts), 128.79 (C*m*-Ph), 129.31 (C*m*-Ts), 136.77 and 137.98 (C*i*-Ts, C*i*-Ph), 144.26 (C*p*-Ts), 149.57 (N*C*O$_2$-*t*Bu), 168.69 and 169.14 (*C*O$_2$-*t*Bu, C-5) ppm. $C_{27}H_{34}N_2O_7S$ (530.64): calcd. C 61.11, H 6.46, N 5.28, S 6.04; found C 61.17, H 6.63, N 4.74, S 6.21. HPLC (A/B, 80:1): t_R = 6.90 min.

General Procedure for Reduction of Compounds 5–8 and 10: BH_3 complex was added dropwise to a stirred solution of substrate **5**–**8** or **10** in THF at 0 °C under an atmosphere of argon. The reaction mixture was kept for 0.5 h at 0 °C under an argon atmosphere, then for 3–35 d at the appropriate temperature. MeOH was then added dropwise to the reaction mixture until foaming stopped. The reaction mixture was evaporated to dryness. The residue was subjected to column flash chromatography (benzene/EtOAc) to isolate the reaction products.

Methyl (2*S*,4*S*)-4-(4-Methylbenzenesulfonyl)amino-1-phenylprolinate (11): BH_3·Me_2S (0.2 mL, 2.09 mmol) was added to a solution of compound **5** (200 mg, 0.52 mmol) in dry THF (2 mL). The reaction mixture was kept for 3 d at –5 °C. Column flash chromatography gave compound **11** (85 mg, 44%) as a colorless amorphous solid. $[\alpha]_D$ = –65.6 (*c* = 2.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.96 (ddd, *J* = 14.0, 2.8, 1.6 Hz, 1 H, 3-H^B), 2.38 (ddd, *J* = 14.0, 9.9, 6.3 Hz, 1 H, 3-H^A), 2.44 (s, 3 H, Me-Ts), 3.39 (ddd, *J* = 10.2, 2.2, 1.2 Hz, 1 H, 5-H^B), 3.43 (dd, *J* = 10.2, 5.0 Hz, 1 H, 5-H^A), 3.79 (s, 3 H, OMe), 4.14 (dd, *J* = 9.9, 1.6 Hz, 1 H, 2-H), 4.19 (m, 1 H, 4-H), 6.06 (d, *J* = 10.2 Hz, 1 H, NH), 6.43 (dd, ^3J = 8.8, 1.0 Hz, 2 H, H*o*-Ph), 6.77 (tt, ^3J = 7.3, 1.0 Hz, 1 H, C*p*-Ph), 7.21 (dd, ^3J = 8.8, 7.3 Hz, 2 H, H*m*-Ph), 7.31 (d, *J* = 8.3, Hz, 2 H, H*m*-Ts), 7.77 (d, *J* = 8.1 Hz, 2 H, H*o*-Ts) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.53 (Me-Ts), 36.42 (C-3), 52.79 (C-4 and CO_2*Me*), 55.18 (C-5), 59.73 (C-2), 112.30 (C*o*-Ph), 117.95 (C*p*-Ph), 126.95 (C*o*-Ts), 129.38 (C*m*-Ph), 129.79 (C*m*-Ts), 138.21 (C*i*-Ts), 143.46 (C*p*-Ts), 145.94 (C*i*-Ph), 175.77 (*C*O$_2$Me) ppm. $C_{19}H_{22}N_2O_4S$ (374.46): calcd. C 60.94, H 5.92, N 7.48; found C 61.30, H 6.19, N 7.34. RP-HPLC–MS [Supelcosil LC-18; MeCN/H_2O, 1:1; 1.0 mL/min; t_R = 11.6 min; APCI]: *m*/*z* (%) = 375 (100) [M + H]$^+$; 373 (100) [M – H]$^–$. HPLC (A/B, 40:1): t_R = 7.9 min.

***tert*-Butyl (2*S*,4*S*)-4-(4-Methylbenzenesulfonyl)amino-1-phenylprolinate (12):** BH_3·Me_2S (0.18 mL, 1.87 mmol) was added to a solution of compound **10** (200 mg, 0.46 mmol) in dry THF (2 mL). The reaction mixture was kept for 7 d at –5 °C. Column flash chromatography gave a 96:4 mixture (100 mg) of ester **12** and ether **15**, respectively, according to ^{1}H NMR spectroscopy and HPLC data. Column flash chromatography (hexane/EtOAc) of that mixture gave compound **12** (80 mg, 43%) as a colorless amorphous solid. $[\alpha]_D$ = –66.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 (s, 9 H, *t*Bu), 1.90 (dm, *J* = 14.0 Hz, 1 H, 3-H^B), 2.34 (ddd, *J* = 14.0, 9.9, 6.3 Hz, 1 H, 3-H^A), 2.44 (s, 3 H, Me-Ts), 3.37 and 3.40 (ABX system, J_{AB} = 10.1 Hz, J_{AX} = 4.4 Hz, J_{BX} = 2.6 Hz, 2 H, 5-H^B and 5-H^A), 3.98 (dd, *J* = 9.9, 1.6 Hz, 1 H, 2-H), 4.17 (m, 1 H, 4-H), 6.29 (d, *J* = 10.4 Hz, 1 H, NH), 6.45 (dd, *J* = 8.8, 1.0 Hz, 2 H, H*o*-Ph), 6.75 (tt, ^3J = 7.3, 1.0 Hz, 1 H, H*p*-Ph), 7.20 (dd, *J* = 8.8, 7.3 Hz, 2 H, H*m*-Ph), 7.30 (d, *J* = 8.4 Hz, 2 H, H*m*-Ts), 7.76 (d, *J* = 8.4 Hz, 2 H, H*o*-Ts) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.51 (Me), 27.88 (Me-*t*Bu), 36.39 (C-3), 52.81 (C-4), 55.29 (C-5), 60.99 (C-2), 82.96 (C-*t*Bu), 112.29 (C*o*-Ph), 117.71 (C*p*-Ph), 126.94 (C*o*-Ts), 129.27 and 129.77 (C*m*-Ts, C*m*-Ph), 138.32 (C*i*-Ts), 143.33 (C*p*-Ts), 146.09 (C*i*-Ph), 174.66 (CO$_2$-*t*Bu) ppm. $C_{22}H_{28}N_2O_4S$ (416.54): calcd. C 63.44, H 6.78, N 6.72; found C 63.56, H 6.88, N 6.76. RP-HPLC–MS [Luna C18(2); MeCN/H_2O, 75:25; 0.25 mL/min; t_R = 3.9 min; ESI]: *m*/*z* (%) = 439 (45) [M + Na]$^+$, 417 (100) [M + H]$^+$, 361 (89) [M – *t*Bu + 2H]$^+$; 415 (100) [M – H]$^–$. HPLC (A/B, 120:1): t_R = 8.1 min.

(2*S*,4*S*)-2-Hydroxymethyl-4-(4-methylbenzenesulfonyl)amino-1-phenylpyrrolidine (13): BH_3·Me_2S (0.68 mL, 7.21 mmol) was added to a solution of compound **5** (0.70 g, 1.80 mmol) in dry THF (10 mL). The reaction mixture was kept for 7 d at 40 °C. Column flash chromatography gave compound **13** (0.45 g, 72%) as colorless crystals. M.p. 142–144 °C. $[\alpha]_D$ = –73.8 (*c* = 1.0, acetone). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.72 (ddd, *J* = 13.9, 2.6, 1.3 Hz, 1 H, 3-H^B), 2.23 (br. m, 1 H, OH), 2.33 (ddd, *J* = 13.9, 9.9, 7.3 Hz, 1 H, 3-H^A), 2.44 (s, 3 H, Me-Ts), 3.36 (dd, *J* = 10.3, 6.0 Hz, 1 H, 5-H^B), 3.48 (dd, *J* = 10.3, 1.2 Hz, 1 H, 5-H^A), 3.50 (dm, *J* = 11.3 Hz, 1 H, 6-H^B), 3.85 (dm, *J* = 9.9, Hz, 1 H, 2-H), 4.03 (m, 1 H, 4-H), 4.12 (dt, *J* = 11.3, 2.4 Hz, 1 H, 6-H^A), 6.54 (d, *J* = 8.7 Hz, 2 H, H*o*-Ph), 6.74 (t, *J* = 7.3 Hz, 1 H, H*p*-Ph), 6.76 (d, *J* = 9.4 Hz, 1 H, NH), 7.21 (dd, ^3J = 8.7, 7.3 Hz, 2 H, H*m*-Ph), 7.31 (d, *J* = 8.1 Hz, 2 H, H*m*-Ts), 7.78 (d, *J* = 8.1 Hz, 2 H, H*o*-Ts) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.52 (Me-Ts), 35.85 (C-3), 51.68 (C-4), 57.40 (C-5), 58.74 (C-2), 62.62 (C-6), 112.73 (C*o*-Ph), 117.34 (C*p*-Ph), 126.96 (C*o*-Ts), 129.37 (C*m*-Ph), 129.75 (C*m*-Ts), 138.35 (C*i*-Ts), 143.24 (C*p*-Ts), 146.90 (C*i*-Ph) ppm. $C_{18}H_{22}N_2O_3S$ (346.45):

calcd. C 62.40, H 6.40, N 8.09, S 9.26; found C 62.42, H 6.47, N 7.94, S 9.52. HPLC (A/B, 40:1): t_R = 16.5 min.

(2*S*,4*S*)-2-Methoxymethyl-4-(4-methylbenzenesulfonyl)amino-1-phenylpyrrolidine (14): A 1 M solution (1.0 mL) of BH_3 in THF was added to a solution of compound **5** (100 mg, 0.26 mmol) in dry THF (1 mL). The reaction mixture was kept for 8 d at 25 °C. Column flash chromatography gave compound **14** (11 mg, 12%) as a pale-yellow amorphous solid. $[\alpha]_D$ = –56.5 (*c* = 1.0, acetone). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.72 (dm, *J* = 13.9 Hz, 1 H, 3-H^B), 2.30 (ddd, *J* = 13.9, 10.1, 7.3 Hz, 1 H, 3-H^A), 2.44 (s, 3 H, Me-Ts), 3.30 (dd, *J* = 10.3, 6.1 Hz, 1 H, 5-H^B), 3.36 (dd, *J* = 9.8, 2.1 Hz, 1 H, 6-H^B), 3.39 (s, 3 H, OMe), 3.41 (dt, *J* = 10.3, 1.4 Hz, 1 H, 5-H^A), 3.80 (dd, *J* = 9.8, 2.4 Hz, 1 H, 6-H^A), 3.87 (dm, *J* = 10.1 Hz, 1 H, 2-H), 4.05 (dddt, *J* = 9.9, 7.3, 6.1, 1.4 Hz, 1 H, 4-H), 6.55 (d, *J* = 8.7 Hz, 2 H, H*o*-Ph), 6.75 (t, *J* = 7.3 Hz, 1 H, H*p*-Ph), 6.78 (d, *J* = 9.9 Hz, 1 H, NH), 7.22 (dd, *J* = 8.7, 7.3 Hz, 2 H, H*m*-Ph), 7.32 (d, *J* = 8.3, Hz, 2 H, H*m*-Ts), 7.77 (d, *J* = 8.3 Hz, 2 H, H*o*-Ts) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.50 (Me-Ts), 35.41 (C-3), 51.67 (C-4), 56.94, 57.94 and 59.28 (OMe, C-5, C-2), 72.86 (C-6), 112.70 (C*o*-Ph), 117.20 (C*p*-Ph), 126.93 (C*o*-Ts), 129.28 and 129.68 (C*m*-Ph, C*m*-Ts), 138.55 (C*i*-Ts), 143.10 (C*p*-Ts), 146.71 (C*i*-Ph) ppm. MS [direct liquid introduction; MeOH, 0.25 mL/min. ESI]: *m*/*z* (%) = 383 (100) $[M + Na]^+$, 329 (14) $[M – OMe]^-$, 359 (100) $[M – H]^-$. $C_{19}H_{24}N_2O_3S$ (360.48). HPLC (A/B, 40:1): t_R = 7.1 min.

(2*S*,4*S*)-2-*tert*-Butyloxymethyl-4-(4-methylbenzenesulfonyl)amino-1-phenylpyrrolidine (15): BH_3·Me_2S (0.17 mL, 1.83 mmol) was added to a solution of compound **10** (197 mg, 0.46 mmol) in dry THF (2 mL). The reaction mixture was kept for 7 d at 25 °C. Column flash chromatography gave compound **15** (70 mg, 38%) as a colorless amorphous solid. $[\alpha]_{578}$ = –46.5 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 (s, 9 H, *t*Bu), 1.70 (dm, *J* = 14.0 Hz, 1 H, 3-H^B), 2.30 (ddd, *J* = 14.0, 10.1, 7.7 Hz, 1 H, 3-H^A), 2.44 (s, 3 H, Me-Ts), 3.26–3.30 (m, 2 H, 5-H^B, 6-H^B), 3.36 (dm, *J* = 10.4 Hz, 1 H, 5-H^A), 3.86–3.93 (m, 2 H, 2-H, 6-H^A), 4.06 (m, 1 H, 4-H), 6.49 (dd, *J* = 8.8, 1.0 Hz, 2 H, H*o*-Ph), 6.70 (tt, *J* = 7.3, 1.0 Hz, 1 H, H*p*-Ph), 7.19 (dd, *J* = 8.8, 7.3 Hz, 2 H, H*m*-Ph), 7.27 (d, *J* = 9.7 Hz, 1 H, NH), 7.31 (d, *J* = 8.4 Hz, 2 H, H*m*-Ts), 7.77 (d, *J* = 8.4 Hz, 2 H, H*o*-Ts) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.52 (Me-Ts), 27.40 (Me-*t*Bu), 35.67 (C-3), 51.66 (C-4), 57.03 and 57.90 (C-5, C-2), 61.75 (C-6), 74.72 (C-*t*Bu), 112.45 (C*o*-Ph), 116.66 (C*p*-Ph), 126.90 (C*o*-Ts), 129.24 and 129.68 (C*m*-Ph, C*m*-Ts), 139.01 (C*i*-Ts), 142.94 (C*p*-Ts), 146.95 (C*i*-Ph) ppm. $C_{22}H_{30}N_2O_3S$ (402.56): calcd. C 65.64, H 7.51, N 6.96; found C 65.84, H 7.54, N 6.92. RP-HPLC–MS [Luna C18(2); MeCN/H_2O, 75:25; 0.25 mL/min; t_R = 4.6 min; ESI]: *m*/*z* (%) = 403 (100) $[M + H]^+$, 347 (16) $[M – t\text{Bu} + 2H]^+$, 401 (100) $[M – H]^-$. HPLC (A/B, 120:1): t_R = 5.9 min.

(2*S*,4*S*)-4-(4-Methylbenzenesulfonyl)amino-1-phenylpyrrolidine-2-carbaldehyde (16): BH_3·Me_2S (0.18 mL, 1.89 mmol) was added to a solution of compound **10** (200 mg, 0.47 mmol) in dry THF (2 mL). The reaction mixture was kept for 35 d at –5 °C. Column flash chromatography gave compound **16** (41 mg, 25%) as an amorphous solid. $[\alpha]_D$ = –122.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.11 (dt, *J* = 13.6, 4.1 Hz, 1 H, 3-H^B), 2.31 (ddd, *J* = 13.6, 9.4, 5.8 Hz, 1 H, 3-H^A), 2.44 (s, 3 H, Me), 3.47 (d, *J* = 4.5 Hz, 2 H, 5-H), 3.97 (m, 1 H, 4-H), 4.07 (ddd, *J* = 9.4, 4.1, 2.5 Hz, 1 H, 2-H), 5.08 (d, *J* = 6.4 Hz, 1 H, NH), 6.47 (d, *J* = 7.8 Hz, 2 H, H*o*-Ph), 6.79 (t, *J* = 7.4 Hz, 1 H, H*p*-Ph), 7.21 (dd, *J* = 8.7, 7.4 Hz, 2 H, H*m*-Ph), 7.32 (d, *J* = 8.4 Hz, 2 H, H*m*-Ts), 7.76 (d, *J* = 8.4 Hz, 2 H, H*o*-Ts), 9.59 (d, *J* = 2.5 Hz, 1 H, CHO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.51 (Me), 34.42 (C-3), 52.19 (C-4), 54.92 (C-5), 65.71 (C-2), 112.39 (C*o*-Ph), 118.17 (C*p*-Ph), 127.10 (C*o*-Ts), 129.44 and 129.90 (C*m*-Ph, C*m*-Ts), 136.87 (C*i*-Ts), 143.88 (C*p*-Ts), 146.39 (C*i*-Ph), 203.24 (CHO) ppm. $C_{18}H_{20}N_2O_3S$ (344.43): calcd. C 62.77, H 5.85, N 8.13; found C 62.78, H 6.21, N 7.75. HPLC (A/B, 40:1): t_R = 8.2 min.

Methyl (2*S*,4*S*)-1-Phenyl-4-phthalimidoprolinate (17), (2*S*,4*S*)-2-Hydroxymethyl-1-phenyl-4-phthalimidopyrrolidine (18), Methyl (2*S*,4*S*)-4-(2,3-Dihydro-3-oxo-1*H*-isoindol-2-yl)-1-phenylprolinate (19), and (2*S*,4*S*)-4-(2,3-Dihydro-3-oxo-1*H*-isoindol-2-yl)-2-hydroxymethyl-1-phenylpyrrolidine (20): BH_3·Me_2S (0.49 mL, 5.17 mmol) was added to a solution of compound **6** (0.47 g, 1.29 mmol) in dry THF (10 mL). The reaction mixture was kept for 7 d at 25 °C. Column flash chromatography gave ester **17** (118 mg, 26%), a 26:74 (according to ^{1}H NMR spectroscopy and HPLC and LCMS data, 163 mg) mixture of prolinol **18** and ester **19**, and compound **20** (44 mg, 11%).

Methyl (2*S*,4*S*)-1-Phenyl-4-phthalimidoprolinate (17): Pale-yellow crystals. M.p. 122–124 °C. $[\alpha]_D$ = –40.3 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.73 (dt, *J* = 12.6, 8.3, Hz, 1 H, 3-H^B), 2.99 (ddd, *J* = 12.6, 9.9, 7.5 Hz, 1 H, 3-H^A), 3.74 (s, 3 H, CO_2Me), 3.78 (dd, *J* = 8.6, 8.3 Hz, 1 H, 5-H^B), 4.02 (dd, *J* = 9.0, 8.6 Hz, 1 H, 5-H^A), 4.51 (dd, *J* = 8.2, 7.5 Hz, 1 H, 2-H), 4.94 (ddt, *J* = 9.9, 9.0, 8.3 Hz, 1 H, 4-H), 6.57 (dd, *J* = 8.8, 1.0 Hz, 2 H, H*o*-Ph), 6.76 (tt, *J* = 7.3, 1.0 Hz, 1 H, H*p*-Ph), 7.23 (dd, *J* = 8.8, 7.3 Hz, 2 H, H*m*-Ph), 7.74 (m, 2 H, Phth), 7.86 (m, 2 H, Phth) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.17 (C-3), 47.81 and 49.58 (C-4, C-5), 52.30 (CO_2*Me*), 59.51 (C-2), 112.33 (C*o*-Ph), 117.58 (C*p*-Ph), 123.36 (C*o*-Phth), 129.21 (C*m*-Ph), 131.74 (C*m*-Phth), 134.21 (C*i*-Phth), 146.25 (C*i*-Ph), 167.96 (CO-Phth), 173.68 (*C*O_2Me) ppm. RP-HPLC–MS [Supelcosil LC-18; MeOH/H_2O, 6:4; 1.0 mL/min; t_R = 12.3 min; APCI]: *m*/*z* (%) = 351 (100) $[M + H]^+$, 367 (100) $[M – H + H_2O]^-$. $C_{20}H_{18}N_2O_4$ (350.37): calcd. C 68.56, H 5.18, N 7.99; found C 68.34, H 5.06, N 7.79. HPLC (A/B, 20:1): t_R = 5.5 min.

(2*S*,4*S*)-2-Hydroxymethyl-1-phenyl-4-phthalimidopyrrolidine (18): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.11 (br. m, 1 H, OH), 2.50 (ddd, *J* = 12.7, 9.0, 7.4 Hz, 1 H, 3-H^B), 2.86 (ddd, *J* = 12.7, 10.0, 7.3 Hz, 1 H, 3-H^A), 3.67 (t, *J* = 9.0 Hz, 1 H, 5-H^B), 3.76–3.79 (m, 1 H, 6-H^B), 3.99–4.03 (m, 2 H, 6-H^A), 4.01 (t, *J* = 9.0 Hz, 1 H, 5-H^A), 4.16 (m, 1 H, 2-H), 4.92 (m, 1 H, 4-H), 6.71 (d, *J* = 8.7 Hz, 2 H, H*o*-Ph), 6.76 (t, *J* = 7.4 Hz, 1 H, H*p*-Ph), 7.24 (dd, *J* = 8.7, 7.4 Hz 2 H, H*m*-Ph), 7.74 (m, 2 H, Phth), 7.86 (m, 2 H, Phth) ppm. RP-HPLC–MS [Supelcosil LC-18; MeOH/H_2O, 7:3; 1.0 mL/min; t_R = 5.8 min; APCI]: *m*/*z* (%) = 323 (100) $[M + H]^+$, 339 (100) $[M – H + H_2O]^-$. HPLC (A/B, 20:1): t_R = 13.0 min.

Methyl (2*S*,4*S*)-4-(2,3-Dihydro-3-oxo-1*H*-isoindol-2-yl)-1-phenylprolinate (19): 3 M NaOH (0.05 mL) was added to a solution of a mixture of compounds **18** and **19** (163 mg) in acetone (1 mL). The reaction mixture was kept for 1 h at 5 °C and diluted with water. The precipitate was filtered off, washed with water, dried, and reprecipitated from EtOAc solution with hexane to give compound **19** (79 mg, 28%) as colorless needles. M.p. 160–162 °C. $[\alpha]_D$ = –31.2 (*c* = 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (ddd, *J* = 13.4, 6.6, 5.8 Hz, 1 H, 3-H^B), 2.85 (ddd, *J* = 13.4, 9.1, 7.8 Hz, 1 H, 3-H^A), 3.70 (s, 3 H, CO_2Me), 3.74 (dd, *J* = 9.8, 6.5 Hz, 1 H, 5-H^B), 3.77 (dd, *J* = 9.8, 7.0 Hz, 1 H, 5-H^A), 4.38 (dd, *J* = 9.1, 5.8 Hz, 1 H, 2-H), 4.50 (d, *J* = 17.0 Hz, 1 H, CH^B-Ar), 4.58 (d, *J* = 17.0 Hz, 1 H, CH^A-Ar), 5.18 (dddd, *J* = 7.8, 7.0, 6.6, 6.4 Hz, 1 H, 4-H), 6.59 (dd, *J* = 8.8, 1.0 Hz, 2 H, H*o*-Ph), 6.80 (tt, *J* = 7.4, 1.0 Hz, 1 H, H*p*-Ph), 7.25 (dd, *J* = 8.8, 7.4 Hz, 2 H, H*m*-Ph), 7.47 (m, 2 H, Ar), 7.55 (m, 1 H, Ar), 7.86 (m, 1 H, 4′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.85 (C-3), 46.68 and 49.62 (C-4, C-5),

51.31 and 52.31 (CO_2Me, CH_2-Ar), 59.83 (C-2), 112.76 (C*o*-Ph), 118.07 (C*p*-Ph), 122.84, 123.61 and 128.07 (Ar), 129.31 (C*m*-Ph), 131.55, 132.35 and 141.29 (Ar), 146.40 (C*i*-Ph), 168.91 (*C*O-Ar), 174.22 (*C*O_2Me) ppm. RP-HPLC–MS [Supelcosil LC–18, MeCN/H_2O, 97:3, 1.2 mL/min; t_R = 2.5 min; APCI]: *m*/*z* (%) = 337 (100) $[M + H]^+$, 303 (100) $[M – H – MeOH]^-$, 335 (7) $[M – H]^-$. $C_{20}H_{20}N_2O_3$ (336.39): calcd. C 71.41, H 5.99, N 8.33; found C 71.42, H 5.84, N 8.52. HPLC (A/B, 20:1): t_R = 15.2 min.

(2*S*,4*S*)-4-(2,3-Dihydro-3-oxo-1*H*-isoindol-2-yl)-2-hydroxymethyl-1-phenylpyrrolidine (20): Pale-yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.89 (br. s, 1 H, OH), 2.50 (dd, *J* = 8.9, 7.4 Hz, 2 H, 3-H), 3.59 (dd, *J* = 9.5, 8.6 Hz, 1 H, 5-H^B), 3.67 (dm, *J* = 11.3, Hz, 1 H, 6-H^B), 3.76 (dd, *J* = 9.5, 7.9 Hz, 1 H, 5-H^A), 4.02 (dd, *J* = 11.3, 4.4 Hz, 1 H, 6-H^A), 4.09 (tdd, *J* = 7.4, 4.4, 2.2 Hz, 1 H, 2-H), 4.50 (d, *J* = 16.8 Hz, 1 H, CH^B-Ar), 4.56 (d, *J* = 16.8 Hz, 1 H, CH^A-Ar), 4.97 (tdd, *J* = 8.9, 8.6, 7.9 Hz, 1 H, 4-H), 6.71 (d, *J* = 8.7 Hz, 2 H, H*o*-Ph), 6.77 (t, *J* = 7.4 Hz, 1 H, H*p*-Ph), 7.25 (dd, *J* = 8.7, 7.4 Hz, 2 H, H*m*-Ph), 7.45–7.50 (m, 2 H, Ar), 7.56 (m, 1 H, Ar), 7.86 (m, 1 H, Ar) ppm. RP-HPLC–MS [Supelcosil LC-18; MeCN/H_2O, 8:2; 1.0 mL/min; t_R = 3.1 min; APCI]: *m*/*z* (%) = 309 (100) $[M + H]^+$. HPLC (A/B, 20:3): t_R = 11.3 min.

***tert*-Butyl (2*S*,4*S*)-4-(*tert*-Butyloxycarbonyl)amino-1-phenylprolinate (21):** BH_3·Me_2S (0.5 mL, 5.31 mmol) was added to a solution of compound **7** (0.5 g, 1.33 mmol) in dry THF (5 mL). The reaction mixture was kept for 35 d at –5 °C. Column flash chromatography gave compound **21** (370 mg, 77%) as colorless crystals. M.p. 112–114 °C. $[\alpha]_{578}$ = –84.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 9 H, *t*Bu), 1.49 (s, 9 H, *t*Bu), 2.08 (dq, *J* = 13.8, 1.5 Hz, 1 H, 3-H^B), 2.51 (ddd, *J* = 13.8, 10.0, 6.3 Hz, 1 H, 3-H^A), 3.47 (dt, *J* = 9.8, 1.4 Hz, 1 H, 5-H^B), 3.57 (dd, *J* = 9.8, 5.5 Hz, 1 H, 5-H^A), 4.08 (dd, *J* = 10.0, 1.5 Hz, 1 H, 2-H), 4.46 (m, 1 H, 4-H), 5.77 (d, *J* = 9.4 Hz, 1 H, NH), 6.54 (dd, *J* = 8.7, 1.0 Hz, 2 H, H*o*-Ph), 6.76 (tt, *J* = 7.3, 1.0 Hz, 1 H, H*p*-Ph), 7.23 (dd, *J* = 8.7, 7.3 Hz, 2 H, H*m*-Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.86 and 28.40 (both Me-*t*Bu), 37.20 (C-3), 49.77 (C-4), 55.61 (C-5), 61.28 (C-2), 79.31 and 82.26 (both C-*t*Bu), 112.30 (C*o*-Ph), 117.38 (C*p*-Ph), 129.24 (C*m*-Ph), 146.52 (C*i*-Ph), 155.39 (N*C*O_2-*t*Bu), 174.25 (*C*O_2-*t*Bu) ppm. $C_{20}H_{30}N_2O_4$ (362.47): calcd. C 66.27, H 8.34, N 7.73; found C 66.20, H 8.57, N 7.45. HPLC (A/B, 40:1): t_R = 3.5 min.

(2*S*,4*S*)-4-[(*tert*-Butyloxycarbonyl)(4-methylbenzenesulfonyl)amino]-2-hydroxymethyl-1-phenylpyrrolidine (22) and (2*S*,4*S*)-4-[(*tert*-Butyloxycarbonyl)(4-methylbenzenesulfonyl)amino]-2-*tert*-butyloxymethyl-1-phenylpyrrolidine (23): BH_3·Me_2S (0.13 mL, 1.41 mmol) was added to a solution of compound **8** (188 mg, 0.35 mmol) in dry THF (2 mL). The reaction mixture was kept for 24 d at 40 °C. After evaporation to dryness under reduced pressure the residue was subjected to column flash chromatography (hexane/*i*BuOH) to give compound **23** (85 mg, 48%), a 4:1 (according to ^{1}H NMR spectroscopy) mixture of compounds **22** and **13** (23 mg), and compound **13** (10 mg, 14%).

(2*S*,4*S*)-4-[(*tert*-Butyloxycarbonyl)(4-methylbenzenesulfonyl)amino]-2-hydroxymethyl-1-phenylpyrrolidine (22): RP-HPLC–MS [Luna C18(2); MeCN/H_2O, 7:3; 0.3 mL/min; t_R = 3.5 min; ESI]: *m*/*z* (%) = 469 (3.6) $[M + Na]^+$, 447 (100) $[M + H]^+$, 391 (4.9) $[M – t\text{Bu} + 2H]^+$, 347 (39) $[M – Boc + 2H]^+$. HPLC (A/B, 40:1): t_R = 10.4 min.

(2*S*,4*S*)-4-[(*tert*-Butyloxycarbonyl)(4-methylbenzenesulfonyl)amino]-2-*tert*-butyloxymethyl-1-phenylpyrrolidine (23): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (s, 9 H, *t*Bu), 1.37 (s, 9 H, Me-Boc), 2.45 (s, 3 H, Me-Ts), 2.51 (ddd, *J* = 12.3, 10.4, 6.9 Hz, 1 H, 3-H^B), 2.58 (ddd, *J* = 12.3, 8.9, 7.8 Hz, 1 H, 3-H^A), 3.23 (dd, *J* = 8.9, 8.7 Hz, 1 H, 6-H^B), 3.62 (t, *J* = 8.6 Hz, 1 H, 5-H^B), 3.78 (dd, *J* = 8.6, 3.6 Hz, 1 H, 6-H^A), 3.88 (t, *J* = 8.9 Hz, 1 H, 5-H^A), 4.01 (dddd, *J* = 8.9, 7.8, 6.9, 3.6 Hz, 1 H, 2-H), 5.08 (dq, *J* = 10.4, 8.9 Hz, 1 H, 4-H), 6.67 (d, *J* = 8.6 Hz, 2 H, H*o*-Ph), 6.71 (t, *J* = 7.3 Hz, 1 H, H*p*-Ph), 7.23 (dd, *J* = 8.6, 7.3 Hz, 2 H, H*m*-Ph), 7.33 (d, *J* = 8.1 Hz, 2 H, H*m*-Ts), 7.76 (d, *J* = 8.1 Hz, 2 H, H*o*-Ts) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.58 (Me-Ts), 27.54 (Me-*t*Bu), 27.84 (Me-Boc), 33.44 (C-3), 50.68 (C-5), 54.67 (C-4), 56.70 (C-2), 63.08 (C-6), 73.02 (C-*t*Bu), 84.69 (C-Boc), 113.05 (C*o*-Ph), 116.60 (C*p*-Ph), 127.45 (C*o*-Ts), 129.20 (C*m*-Ph), 129.37 (C*m*-Ts), 137.65 (C*i*-Ts), 144.10 (C*p*-Ts), 146.99 (C*i*-Ph), 150.14 (CO-Boc) ppm. RP-HPLC–MS [Luna C18(2); MeOH/H_2O, 8:2; 0.25 mL/min; t_R = 13.6 min; ESI]: *m*/*z* (%) = 525 (5) $[M + Na]^+$, 503 (100) $[M + H]^+$, 447 (5) $[M – Boc + 2Na]^+$, 425 (1) $[M – Boc + H + Na]^+$, 403 (10) $[M – Boc + 2H]^+$, 347 (18) $[M – Ts]^+$. HPLC (A/B, 80:1): t_R = 3.3 min.

(2*S*,4*S*)-4-[(*tert*-Butyloxycarbonyl)(4-methylbenzenesulfonyl)amino]-2-*tert*-butyloxymethyl-5-oxo-1-phenylpyrrolidine (24): BH_3·Me_2S (0.12 mL, 1.31 mmol) was added to a solution of compound **8** (173 mg, 0.33 mmol) in dry THF (2 mL). The reaction mixture was kept for 35 d at 25 °C. After evaporation to dryness under reduced pressure the residue was subjected to column flash chromatography (hexane/*i*BuOH) to give 0.65:1 mixture (49 mg) of compounds **8** and **24**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (s, 9 H, *t*Bu), 1.33 (s, 9 H, Me-Boc), 2.38 (m, 1 H, 3-H^B), 2.41 (s, 3 H, Me-Ts), 2.80 (ddd, *J* = 12.3, 9.8, 7.2 Hz, 1 H, 3-H^A), 3.34 (dd, *J* = 8.9, 7.2 Hz, 1 H, 6-H^B), 3.55 (dd, *J* = 8.9, 4.3 Hz, 1 H, 6-H^A), 4.29 (m, 1 H, 2-H), 5.33 (dd, *J* = 10.2, 9.8 Hz, 1 H, 4-H), 7.22–7.39 (m, 7 H, Ph, Ts), 8.06 (d, *J* = 7.7 Hz, 2 H, Ts) ppm. RP-HPLC–MS [Luna C18(2), MeOH/H_2O, 8:2, 0.25 mL/min; t_R = 4.6 min; APCI]: *m*/*z* (%) = 517 (6) $[M + H]^+$, 417 (69) $[M – Boc]^+$, 361 (100) $[M – Ts]^+$. HPLC (A/B, 80:1): t_R = 6.4 min.

X-ray Analysis: Data for compounds **8**, **13**, **21**, and **23** were collected with an XCALIBUR-3 diffractometer (CCD) by using graphite-monochromated Mo-K_α radiation. Absorption and anomalous dispersion effects were not taken into consideration due to its insignificance. The structures were solved by direct methods and expanded by using Fourier techniques. Refinement of the structure was accomplished with the SHELXL-97 program. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms involved in hydrogen bonding were located in electron density maps. The remainder of the hydrogen atoms were placed in idealized positions and allowed to ride on the C atoms to which they are bonded. CCDC-803760 (for **8**), -803761 (for **13**), -803762 (for **21**), and -803763 (for **23**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystal Data for 8: M_r = 530.62; 0.34 × 0.21 × 0.06 mm; colorless plate; *T* = 295 K; orthorhombic; space group $P2_12_12_1$; *Z* = 4; *a* = 10.5475(7) Å, *b* = 12.1445(9) Å, *c* = 22.4485(13) Å, $\alpha = \beta = \gamma$ = 90.00°, *V* = 2875.5(3) Å^3; $\rho_{calcd.}$ = 1.226 g cm^{-3}; Θ_{max} = 26.38°; R_1 = 3.79% [$I > \sigma(I)$], wR_2 = 4.54%, *S* = 0.984.

Crystal Data for 13: M_r = 346.44; 0.38 × 0.18 × 0.07 mm; colorless needle; *T* = 295 K; monoclinic, space group $P2_1$; *Z* = 2; *a* = 9.718(3) Å, *b* = 7.974(3) Å, *c* = 11.531(3) Å, $\alpha = \gamma$ = 90.0° β = 104.19(2)°, *V* = 866.3(4) Å^3; $\rho_{calcd.}$ = 1.328 g cm^{-3}; Θ_{max} = 26.39°; R_1 = 4.18% [$I > \sigma(I)$], wR_2 = 2.61%, *S* = 0.813.

Crystal Data for 21: M_r = 362.46; 0.43 × 0.27 × 0.14 mm; colorless prism; *T* = 295 K; orthorhombic, space group $P2_12_12_1$; *Z* = 4; *a* = 6.3189(4) Å, *b* = 9.0566(5) Å, *c* = 35.412(2) Å, $\alpha = \beta = \gamma$ = 90.0°,

V = 2026.5(2) Å^3; $\rho_{calcd.}$ = 1.188 g cm^{-3}; Θ_{max} = 26.36°; R_1 = 3.05% [$I > \sigma(I)$], wR_2 = 2.90%, S = 1.006.

Crystal Data for 23: M_r = 502.65; 0.34 × 0.18 × 0.09 mm; colorless prism; T = 120 K; monoclinic, space group $P2_1$; Z = 4; a = 10.5799(8) Å, b = 10.0648(9) Å, c = 25.178(2) Å, $\alpha = \gamma$ = 90.0°, β = 90.146(6)°, V = 2681.1(4) Å^3; $\rho_{calcd.}$ = 1.245 g cm^{-3}; Θ_{max} = 26.37°; R_1 = 3.95% [$I > \sigma(I)$], wR_2 = 3.43%, S = 0.849.

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