Highly Enantioselective Synthesis of Orthogonally Protected (2*S*)-2,3-Diaminopropanoates through Catalytic Phase-Transfer Aza-*Henry* Reaction

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The syntheses of enantiomer-enriched orthogonally protected different (2*S*)-2,3-diaminopropanoates and unnatural furyl-substituted (*tert*-butoxy)carbonyl (Boc) as well as (benzyloxy)carbonyl (Cbz) protected amino acid esters are accomplished by means of an enantioselective aza-*Henry* reaction. A key feature of this protocol is organocatalysis as a genesis of chirality to ensure high enantioselectivity.

Introduction. – The nonproteinogenic α,β-diamino acids (DAPS) have received renewed attention due to their incorporation into peptides which are used to modulate secondary and tertiary conformation [1]. Furthermore, such peptides resist proteolysis [2]. In addition, the active ingredients derived from these α,β-diamino acids display a wide range of pharmaceutical activities as insulinotropic, antidyslipidemic, and antihyperglycemic agent [3] (see **1**–**4** in *Fig. 1*). Some α,β-diamino acid derivatives are protein-tyrosine kinase inhibitors and glycoprotein IIb/IIIa receptor antagonists [4a,b]. Furthermore, α,β-diamino acids are part of several β-lactam antibiotics [4c].

(2*S*)-2,3-Diaminopropanoic acid has been also used to surrogate natural amino acids, *i.e.*, lysine, to investigate the size effect of the side chain on the stability of α-helix formation in simple polypeptides. Additionally, compounds derived from nonproteinogenic α,β-diamino acids such as TAN-1057A (**3**) and TAN-1057B (**4**) were found to be dipeptide antibiotics with potent activity against MRSA [5] (*Fig. 1*).

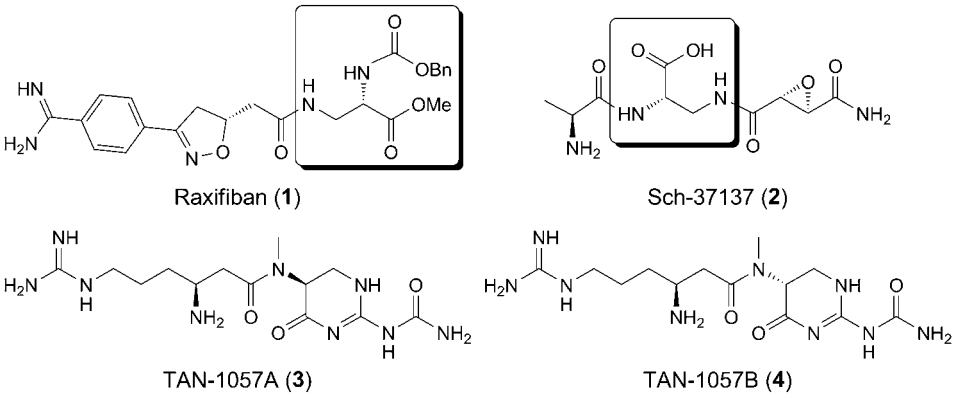


Fig. 1. *Pharmaceutically active α,β-diamino acid derivatives*

α,β-Diamino esters **5a**, **5b**, **6a**, and **6b** (*Fig. 2*) have been regarded as attractive prominent synthetic targets in view of their various biological activities. The development of simple and efficient methods for the synthesis of enantiomerically pure DAPS from readily available starting materials is always a demanding task. A number of enantioselective synthetic methods for the synthesis of diaminopropanoic acids have been reported thus far [6]. They have been commonly prepared by the *Hoffman* and *Curtius* rearrangement of protected asparagine by using trivalent iodine such as bis(trifluoroacetoxy)iodobenzene (= bis(trifluoroacetato-κ0)phenyliodine), the *Mitsunobu* reaction of serine, and the *Schmidt* reaction of aspartic acid [7].

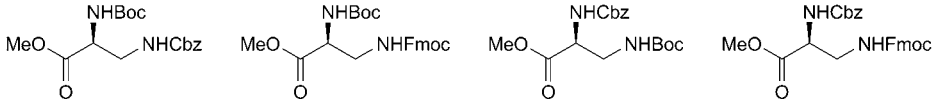
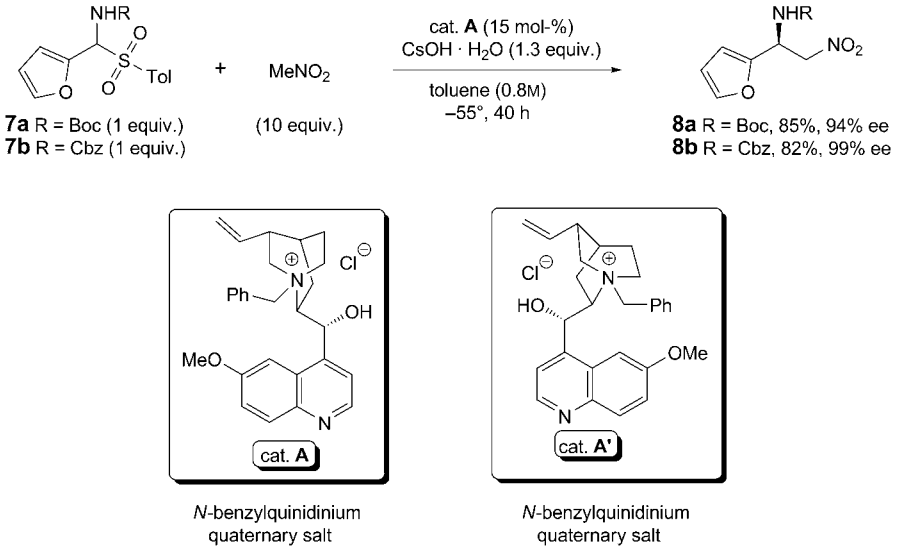


Fig. 2. *Target α,β-diamino acid esters*

A variety of other prominent methods includes the conjugate addition of homochiral lithium *N*-benzyl-*N*-(α-methylbenzyl)amide to α,β-unsaturated esters, *in situ* amination with trisyl azide (=2,4,6-triisopropylbenzenesulfonyl azide), hydrogenation of diastereoisomeric enamides, *Sharpless* asymmetric aminohydroxylation of α,β-unsaturated esters, and aziridine ring opening with azide [8]. The genesis of chirality in the above synthetic strategies is either from the chiral pool or initiated through catalytic asymmetric transformations. Herein, we report an alternative synthetic strategy for the synthesis of α,β-diamino esters **5a**, **5b**, **6a**, and **6b** (*Fig. 2*) by means of a catalytic aza-*Henry* reaction.

Results and Discussion. – The aza-*Henry* reaction is a powerful synthetic transformation that allows creation of a C–C bond bearing vicinal NO_2 and NH_2 functional groups and considered to be a key protocol for the synthesis of N-containing chiral natural products and pharmaceuticals [9]. The asymmetric aza-*Henry* reaction under phase-transfer catalysis (PTC) is established to be the most consistent reaction to induce chirality with high enantioselectivity. In principle, the stereogenic center in **5a**, **5b**, **6a**, and **6b** could be accessed through a catalytic asymmetric aza-*Henry* reaction under PTC conditions by employing *N*-Boc-furylamines **7a** and 7**b** [10] and $MeNO_2$ (Boc = (*tert*-butoxy)carbonyl). We chose the furyl moiety as a masked carboxylic acid as well as to enhance its solubility and to induce high enantioselectivity of the desired product. Consequently, the reaction of **7a** with $MeNO_2$ (10 equiv.), in the presence of quininium catalyst **A** (12 mol-%) and 1.3 equiv. of $CsOH \cdot H_2O$ at $-45°$ for 30 h led to **8a** in 85% yield with 82% enantiomer excess (ee) [11]. For further enantiomer enrichment of the product **8a**, the reaction conditions were optimized by varying the amount of catalyst and the temperature. After considerable experimentation, we accomplished that increasing the catalyst loading from 12 to 15 mol-% and lowering the temperature ($-55°$) and in the presence of $CsOH \cdot H_2O$ (1.3 equiv.) for 40 h furnished **8a** with 94% ee without compromising the yield (*Scheme 1*). The ee of the desired product was confirmed by chiral HPLC.

Scheme 1



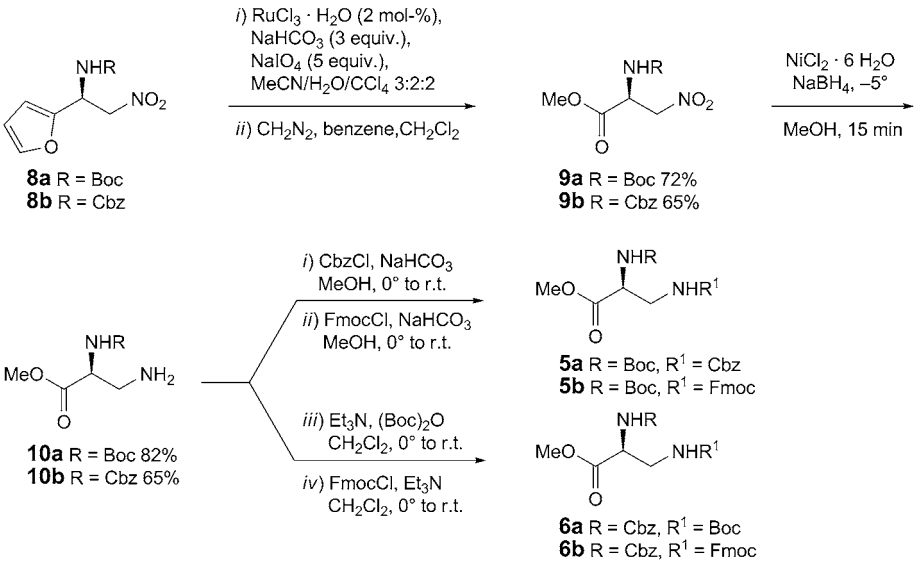
It was anticipated that in the presence of diastereoisomeric quinidinium quaternary salt **A′** as catalyst, the antipode of **8a** would be formed. With catalyst **A′** in place of **A** under otherwise identical conditions as above, *ent*-**8a** with 40% ee in 85% yield was obtained. Surprisingly, cinchonine salt also did not improve the ee of *ent*-**8a** [11].

Having prepared the *N*-Boc-protected *β*-nitroamine **8a**, we next proceeded to synthesize **8b**. To this end, the *N*-Cbz-aminosulfone **7b** (Cbz = (benzyloxy)carbonyl) was subjected to the aza-*Henry* reaction in the presence of catalyst **A**, and under identical conditions as for **8a**, this led to the nitro compound **8b** with 99% ee. The ee of **8b** was ascertained by HPLC with respect to the racemic compound (*Chiralpak OD-H*, hexane/EtOH 7:3, 220 nm).

With the optically active compounds **8a** and **8b** in hand, we advanced further. To this end, the furan moiety of **8a** was oxidatively cleaved ($RuCl_3/NaIO_4$) to afford the carboxylic acid, which was subjected to esterification with CH_2N_2 to give **9a** in 72% yield (two steps) (*Scheme 2*). The NO_2 functionality was converted to the primary amine by $NaBH_4$ in the presence of $NiCl_2 \cdot 6\,H_2O$, and subsequent protection with CbzCl under basic conditions resulted in **5a** in 82% yield. The optical yield of **5a** was established by comparing the magnitude of its optical rotation with that reported in [6a]. The reaction of **10a** with FmocCl (Fmoc = (9*H*-fluoren-9-ylmethoxy)carbonyl) in the presence of base furnished Fmoc-protected **5b** in 62% yield (*Scheme 2*).

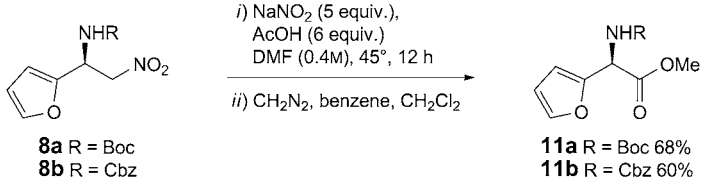
Similarly, the reduction of the NO_2 group of **9b** was achieved with $NiCl_2 \cdot 6\,H_2O/NaBH_4$, and protection of the resulting amino group of **10b** with $(Boc)_2O$ led to **6a** in 68% yield (*Scheme 2*). The crude amino derivative **10b** was protected with FmocCl under basic conditions to give **6b** in good yield. The optical yields of the **6a** and **6b** were established by comparing their magnitude of the optical rotation, respectively, with that reported in [6a].

Scheme 2



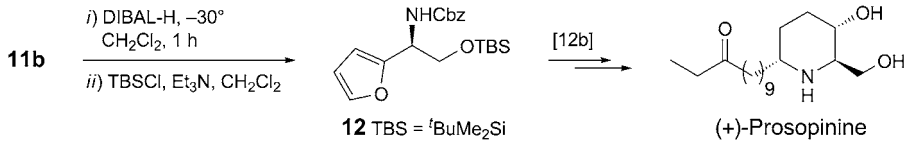
En route to the synthesis of unnatural protected heterocyclic amino acids for our ongoing project, we envisioned to convert the optically pure intermediates **8a** and **8b** into the desired amino acids [12]. Therefore, the nitro derivatives **8a** and **8b** were subjected to oxidation under *Nef* conditions ($NaNO_2$/DMF) leading to the corresponding acids. Following esterification of the crude acids resulted in Boc-protected furylglycine methyl ester **11a** and the Cbz-protected analog **11b**, respectively, in good yields (*Scheme 3*).

Scheme 3



In the course of exploring the synthetic applications of furyl-substituted intermediate **11b**, together with our interest in stereoselective synthesis, prompted us to explore supplementary utility. Hence, **11b** was reduced with DIBAL-H (diisobutylaluminium hydride) at $-30°$ in CH_2Cl_2 followed by protection of the primary alcohol with (*tert*-butyl)dimethylsilyl chloride to give the silyl ether derivative **12**. According to [13b], aza-*Achamotowicz* reaction of **12** led to a key intermediate for the synthesis of the alkaloid (+)-prosopinine (*Scheme 4*). The same intermediate has also been employed for the synthesis of D- and L-deoxymannojirimycin [13a], and (+)-spectaline [13c].

Scheme 4



Conclusions. – In conclusion, we have synthesized different orthogonally protected (2*S*)-2,3-diaminopropanoates in up to 55% overall yield *via* a modified aza-*Henry* reaction. The present protocol was also employed for the preparation of enantiomer-enriched unnatural furyl substituted Boc- and Cbz-protected amino acid esters, respectively, which are considered to be key intermediates for the synthesis of compounds exhibiting anticancer, anti-HIV, and glycosidase-inhibitory activity. Additionally, the application of this methodology is currently under progress for the synthesis of bioactive natural and unnatural products.

We are grateful to Dr. *J. S. Yadav*, Director, IICT, for his constant encouragement. Financial support was provided by the *DST*, New Delhi, India (Grant No: SR/SI/OC-12/2007), and *UGC* (New Delhi) is gratefully acknowledged for awarding the fellowship to *A. P.* Thanks are also due to Dr. *G. V. M. Sharma* for his support.

Experimental Part

General. CH_2Cl_2 was distilled from P_2O_5, THF from Na benzophenone ketyl. All other chemicals used were commercially available. All reactions were conducted under N_2 (*IOLAR*, grade I). Progress of the reactions was monitored by TLC on pre-coated silica gel *60* F_{254} plates (SiO_2, *Merck*). Column chromatography (CC): SiO_2 grade *60–120* and 100–200 mesh. Optical rotations: *Horiba* high-sensitive polarimeter; 10 mm cell. IR Spectra: *Thermo-Nicolet-FT/IR-5700* instrument; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Varian 200* and *500* or *Bruker 300* and *400* at 300, 400, or 500 MHz (^1H) and 75 or 100 MHz (^{13}C); in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, J in Hz. ESI- and HR-MS: quadrupole time-of-flight (QTOF) mass spectrometer *QSTAR XL* (*Applied Biosystems MDSSciex*, Foster City, USA); in *m/z*.

tert-*Butyl* N-*[(1S)-1-(Furan-2-yl)-2-nitroethyl]carbamate* (**8a**). To *N*-Boc aminosulfone **7a** (1.75 g, 5 mmol) and catalyst **A** (0.342 g, 0.75 mmol) in toluene (0.8M) were added $MeNO_2$ (2.95 g, 50 mmol) and $CsOH \cdot H_2O$ (1.09 g, 6.5 mmol) successively under N_2 at $-55°$. The mixture was stirred vigorously for 40 h at $-55°$. Then, the reaction was quenched with 0.1N HCl (20 ml), and the mixture was slowly allowed to warm to r.t. The aq. layer was extracted with $CHCl_3$ (3×20 ml), the combined org. layer washed with brine (2×10 ml), the extract dried (Na_2SO_4) and concentrated, and the residue purified by CC (SiO_2, hexane/AcOEt 8:2): **8a** (1.08 g, 85%). Semi-solid. HPLC (chiral *OD-H* (λ_{max} 220 nm), hexanes/EtOH 85:15, 1 ml/min): 94% ee; t_R (major) 7.7 min, t_R (minor) 10.27 min. $[\alpha]_D^{25} = -23.95$ ($c = 2.10$, $CHCl_3$) ([11c]: $[\alpha]_D^{25} = +17.72$ ($c = 1.50$, $CHCl_3$)). IR (neat): 3311, 1701, 1532, 1507, 1378, 1331, 1249, 1164. ^1H-NMR ($CDCl_3$, 500 MHz): 7.36 (*s*, 1 H); 6.32 (*dd*, $J = 1.6, 3.1$, 1 H); 6.29 (*d*, $J = 3.1$, 1 H); 5.44–5.38 (*m*, 1 H); 5.34 (br. *s*, 1 H); 4.87 (*dd*, $J = 4.5, 12.4$, 1 H); 4.68 (*dd*, $J = 5.5, 12.8$, 1 H); 1.45 (*s*, 9 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 154.2; 148.5; 142.8; 110.6; 107.7; 89.4; 80.8; 47.9; 28.2. ESI-MS: 279 ($[M + Na]^+$). HR-ESI-MS: 279.0963 ($[M + Na]^+$, $C_{11}H_{16}N_2NaO_5^+$; calc. 279.0956).

*Methyl (2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-nitropropanoate* (**9a**). To an ice-cold soln. of $NaIO_4$ (5.2 g, 24.1 mmol) in CCl_4 (20 ml), MeCN (30 ml), and H_2O (20 ml) was added $RuCl_3 \cdot H_2O$ (20 mg, 0.07 mol), and stirring was continued for 15 min at 0°. Then, **8a** (0.896 g, 3.5 mmol) in MeCN (10 ml) was added, and stirring was continued for additional 10 min at 0°. The mixture was quenched with H_2O (10 ml), the aq. layer extracted with AcOEt (3×20 ml), and the combined org. extract washed with

brine (1×15 ml), dried (Na_2SO_4), and concentrated. The crude residue was dissolved in dry CH_2Cl_2 (15 ml) and benzene (5 ml) at 0°. Then, CH_2N_2 in Et_2O (30 mmol) was added. After 3 h of stirring at r.t., the mixture was concentrated and the resulting residue purified by CC (SiO_2, hexane/acetone 85:15): **9a** (0.63 g, 72%). Colorless solid. $[\alpha]_D^{25} = -30.25$ ($c = 1.5$, MeOH) ([6f]: $[\alpha]_D^{25} = -31.0$ ($c = 1$, MeOH)). IR (neat): 3389, 2923, 1718, 1707, 1558, 1501, 1371, 1245, 1134. ^{1}H-NMR ($CDCl_3$, 500 MHz): 5.52 (*d*, $J = 6.5$, 1 H); 4.86 (*dd*, $J = 3.4$, 13.2, 1 H); 4.83 (*dd*, $J = 3.3$, 13.4, 1 H); 4.73–4.61 (*m*, 1 H); 3.85 (*s*, 3 H); 1.46 (*s*, 9 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 168.7; 155.1; 81.0; 75.4; 53.3; 51.3; 28.1. ESI-MS: 271 ($[M + Na]^+$). HR-ESI-MS: 271.0919 ($[M + Na]^+$, $C_9H_{16}N_2NaO_6^+$; calc. 271.0906).

*Methyl (2*S*)-3-{[(Benzyloxy)carbonyl]amino}-2-[(*tert*-butoxy)carbonyl]amino}propanoate* (**5a**). To **9a** (0.50 g, 2 mmol) and $NiCl_2 \cdot 6\,H_2O$ (0.33 g, 2 mmol) in dry MeOH (15 ml) was gradually added $NaBH_4$ (0.38 g, 10 mmol) under N_2 within 10 min at −5°. The mixture was stirred for 15 min, quenched with sat. $NaHCO_3$ soln. (10 ml), and filtered through a *Celite* bed. The filtrate was concentrated, the biphasic mixture extracted with AcOEt (3×10 ml), the org. layer washed with brine, dried (Na_2SO_4), and concentrated, and the resulting crude **10a** (0.37 g, 82%) subjected to the next reaction. To **10a** (0.11 g, 0.5 mmol) in dry CH_2Cl_2 was added $(Boc)_2O$ (0.16 g, 0.75 mmol) and DMAP (= *N*,*N*-dimethylpyridin-4-amine; 5 mg) sequentially at 0°. The mixture was stirred for 5 h at r.t., then quenched with sat. NH_4Cl soln. (5 ml), and extracted with AcOEt (2×10 ml). The extract was washed with brine, dried (Na_2SO_4), and concentrated and the residue purified by CC (SiO_2, hexane/acetone 4:1): **5a** (0.13 g, 74%). Brown oil. $[\alpha]_D^{25} = -18.5$ ($c = 2.0$, $CHCl_3$). IR (neat): 3324, 2922, 2853, 1707, 1501, 1457, 1319, 1211. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.40–7.29 (*m*, 5 H); 5.48 (br. *s*, 1 H); 5.22 (br. *s*, 1 H); 5.09 (*s*, 2 H); 4.45–4.34 (*m*, 1 H); 3.73 (*dd*, $J = 3.7$, 12.2, 1 H); 3.74 (*s*, 3 H); 3.60 (*dd*, $J = 4.3$, 10.6, 1 H); 1.44 (*s*, 9 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 171.5; 167.5; 156.7; 136.2; 128.5; 128.1; 127.8; 66.9; 53.9; 52.6; 42.8; 29.6. ESI-MS: 375 ($[M + Na]^+$). HR-ESI-MS: 375.1539 ($[M + Na]^+$, $C_{17}H_{24}N_2NaO_6^+$; calc. 375.1532).

*Methyl (2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}propanoate* (**5b**). To the crude **10a** (0.11 g, 0.5 mmol) and $NaHCO_3$ (0.11 g, 1.0 mmol) in MeOH was added FmocCl (0.75 mmol) under Ar at 0°. The mixture was stirred for 5 h at r.t. and then concentrated to afford a grayish oil. The grayish oil was dissolved in AcOEt (10 ml), the soln. washed with sat. $NaHCO_3$ soln. (1×5 ml), 1M HCl (1×5 ml), and brine (2×10 ml), dried (Na_2SO_4), and concentrated to afford a white solid. This crude product was partially soluble in CH_2Cl_2. The white solid that did not dissolve in CH_2Cl_2 was filtered off through a *Celite* pad, eluting with CH_2Cl_2. The crude that was obtained after filtration and concentration was further purified by flash CC (SiO_2, hexane/AcOEt 7:3): **5b** (0.13 g, 62%). Semi-solid. $[\alpha]_D^{25} = -12.5$ ($c = 2.0$, MeOH) ([6a]: $[\alpha]_D^{25} = -13.2$ ($c = 1.50$, MeOH)). IR (neat): 3345, 2975, 1690, 1549, 1499, 1365, 1250, 1164. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.77 (*d*, $J = 7.6$, 2 H); 7.61 (*d*, $J = 7.6$, 2 H); 7.42–7.26 (*m*, 6 H); 5.42 (br. *s*, 1 H); 5.19 (*s*, 1 H); 4.38 (*m*, 3 H); 4.21 (*t*, $J = 6.1$, 1 H); 3.74 (*s*, 3 H); 3.62 (*m*, 2 H); 1.44 (*s*, 9 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 172.5; 144.4; 141.5; 137.9; 127.8; 127.6; 127.1; 124.7; 120.1; 73.5; 71.3; 69.6; 65.2; 50.4; 42.8; 31.9; 29.7. ESI-MS: 441 ($[M + H]^+$). HR-ESI-MS: 441.4644 ($[M + H]^+$, $C_{24}H_{28}N_2O_6^+$; calc. 441.4632).

Benzyl N-*[(1*S*)-1-(Furan-2-yl)-2-nitroethyl]carbamate* (**8b**). As described for **8a**, with **7b** (1.92 g, 5 mmol), **A**, toluene, $MeNO_2$, and $CsOH \cdot H_2O$. CC (SiO_2, hexane/AcOEt 9:1) afforded **8b** (1.18 g, 82%). White solid. HPLC (chiral *OD-H* (λ_{max} 220 nm), hexane/EtOH 7:3, 1 ml/min): 99% ee; t_R (major) 11.83 min, t_R (minor) 16.01 min. $[\alpha]_D^{25} = -19.5$ ($c = 2.0$, $CHCl_3$) ([11c]: $[\alpha]_D^{25} = +16.5$ ($c = 1.50$, $CHCl_3$)). IR (neat): 3311, 1701, 1552, 1507, 1378, 1331, 1429. ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.36–7.26 (*m*, 6 H); 6.29 (*dd*, $J = 2.8$, 9.6, 2 H); 6.21 (br. *d*, 1 H); 5.50–5.42 (*m*, 1 H); 5.19 (*s*, 2 H); 4.82 (*dd*, $J = 5.1$, 12.8, 1 H); 4.64 (*dd*, $J = 5.4$, 13.0, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 155.2; 142.8; 142.8; 128.6; 128.4; 128.3; 110.8; 108.1; 96.2 76.2; 67.5; 47.8. ESI-MS: 313 ($[M + Na]^+$). HR-ESI-MS: 313.0803 ($[M + Na]^+$, $C_{14}H_{14}N_2NaO_5^+$; calc. 313.0800).

*Methyl (2*S*)-2-{[(Benzyloxy)carbonyl]amino}-3-nitropropanoate* (**9b**). As described for **9a**, with $NaIO_4$, CCl_4, MeCN, H_2O, $RuCl_3 \cdot H_2O$, **8b** (1.02 g, 3.5 mmol), MeCN (10 ml), and CH_2N_2 in Et_2O (30 mmol): CC (SiO_2, hexane/acetone 4:1) gave **9b** (0.64 g, 65%). White semi-solid. $[\alpha]_D^{25} = -26.2$ ($c = 2.0$, $CHCl_3$). IR (neat): 3364, 2945, 1709, 1549, 1499, 1376, 1256, 1262. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.40–7.33 (*m*, 5 H); 5.79 (br. *s*, 1 H); 5.22 (br. *s*, 1 H); 5.14 (*s*, 2 H); 5.00 (*dd*, $J = 3.2$, 14.7, 1 H); 4.82 (*m*, 2 H); 3.83 (*s*, 3 H); 3.60 (*dd*, $J = 4.3$, 10.6, 1 H); 1.44 (*s*, 9 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 171.5; 167.5;

156.7; 136.2; 128.5; 128.1; 127.8; 66.9; 53.9; 52.6; 42.8; 29.6. ESI-MS: 375 ($[M+Na]^+$). HR-ESI-MS: 305.6532 ($[M+Na]^+$, $C_{12}H_{14}N_2NaO_6^+$; calc. 305.6524).

*Methyl (2S)-2-{[(Benzyloxy)carbonyl]amino}-3-{[(*tert*-butoxy)carbonyl]amino}propanoate* (**6a**). As described for **5a**, with **9b** (0.564 g, 2 mmol), $NiCl_2 \cdot 6\,H_2O$, MeOH, and $NaBH_4$: crude **10b** (0.38 g, 75%). Then as described for **5a**, with **10b** (0.125 g, 0.5 mmol), CH_2Cl_2, $(Boc)_2O$, and DMAP: **6a** (0.11 g, 68%). Brown dense liquid. $[\alpha]_D^{25} = -15.8$ ($c = 2.0$, $CHCl_3$). IR (neat): 3334, 2978, 1726, 1677, 1619, 1536, 1495, 1449, 1370, 1272, 1159, 1094. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.42–7.37 (*m*, 5 H); 6.21 (br. *d*, 1 H); 5.28 (br. *s*, 1 H); 5.22 (*s*, 2 H); 4.24–4.11 (*m*, 1 H); 3.30 (*dd*, $J = 3.2, 10.6$, 1 H); 3.18 (*dd*, $J = 3.4, 9.6$, 1 H); 1.52 (s, 9 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 172.3; 168.1; 159.5; 135.01; 131.41; 128.9; 128.3; 128.1; 127.9; 75.6; 53.7; 42.6; 28.93; 24.40. ESI-MS: 375 ($[M+Na]^+$). HR-ESI-MS: 375.6239 ($[M+Na]^+$, $C_{12}H_{14}N_2NaO_6^+$; calc. 375.6251).

*Methyl (2S)-2-{[(Benzyloxy)carbonyl]amino}-3-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}propanoate* (**6b**). To the crude **10b** (0.12 g, 0.5 mmol) and Et_3N (0.11 g, 1.0 mmol) in CH_2Cl_2 was added FmocCl (0.75 mmol) under Ar at 0°. The mixture was stirred for 3 h at r.t. and then concentrated to afford a semi-solid. The semi-solid was dissolved in AcOEt (10 ml), the org. layer washed with sat. $NaHCO_3$ soln. (1×5 ml), 1M HCl (1×5 ml), and sat. NaCl soln. (2×10 ml), dried (Na_2SO_4), and concentrated to afford a white solid. This crude product was purified by CC (SiO_2, hexane/acetone 7:3): **6b** (0.13 g, 62%). Semi-solid. $[\alpha]_D^{25} = -17.3$ ($c = 2.0$, $CHCl_3$). IR (neat): 3345, 2975, 1690, 1549, 1499, 1365, 1250, 1164. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.79 (*d*, $J = 7.3$, 2 H); 7.66 (*d*, $J = 7.3$, 2 H); 7.42–7.26 (*m*, 11 H); 5.40 (br. *s*, 1 H); 5.10 (*s*, 2 H); 4.37 (*m*, 3 H); 4.18 (*t*, $J = 4.4$, 1 H); 3.68 (*s*, 3 H); 3.64 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 172.7; 157.3; 155.5; 143.6; 142.3; 135.4; 128.3; 127.6; 127.1; 126.3; 120.3; 67.3; 57.4; 51.8; 47.2; 42.8. ESI-MS: 475 ($[M+H]^+$). HR-ESI-MS: 475.1539 ($[M+H]^+$, $C_{17}H_{24}N_2NaO_6^+$; calc. 475.1532).

*Methyl (2R)-2-{[(*tert*-Butoxy)carbonyl]amino}-2-(furan-2-yl)acetate* (**11a**). To the stirred soln. of **8a** (0.51 g, 2 mmol) in DMF/H_2O 7:1 (0.4M) and AcOH (0.60 g, 10 mmol) was added solid $NaNO_2$ (0.83 g, 12 mmol) at r.t. The mixture was heated to 45° for 12 h. Then, the reaction was quenched with H_2O (20 ml), the mixture extracted with CH_2Cl_2 (3×20 ml), and the org. extract washed with H_2O (2×10 ml) and brine (2×10 ml), dried (Na_2SO_4), and concentrated. The crude residue was dissolved in dry CH_2Cl_2 (10 ml) and benzene (2.5 ml) at 0°. To this, CH_2N_2 in Et_2O (20 mmol) was added. After 3 h of stirring at r.t., the mixture was concentrated and the residue purified by CC (SiO_2, hexane/AcOEt 9:1): **11a** (0.35g, 68%). Brown liquid. $[\alpha]_D^{25} = -68.5$ ($c = 2.0$, $CHCl_3$). IR (neat): 3362, 2973, 2924, 2855, 1748, 1499, 1158. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.33 (*t*, $J = 1.3$, 1 H); 6.31 (*dd*, $J = 1.5$, 2 H); 5.40 (br. *s*, 1 H); 3.76 (*s*, 3 H); 1.44 (*s*, 9 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 154.7; 136.9; 128.5; 126.3; 80.4; 78.8; 52.7; 28.1. ESI-MS: 278 ($[M+H]^+$). HR-ESI-MS: 278.1593 ($[M+H]^+$, $C_{12}H_{17}NNaO_5^+$; calc. 278.1582).

Methyl (2R)-2-{[(Benzyloxy)carbonyl]amino}-2-(furan-2-yl)acetate (**11b**). As described for **11a**, with **8b** (0.29 g, 1 mmol), DMF/H_2O 7:1 (0.4M), AcOH (0.30 g, 5 mmol), and $NaNO_2$ (0.42 g, 6 mmol). Quenching with H_2O (10 ml) and extraction with CH_2Cl_2 (3×10 ml). The crude residue in dry CH_2Cl_2 (8 ml) and benzene (1.5 ml) at 0° was treated with CH_2N_2 in Et_2O (10 mmol) as described for **11a**. CC (SiO_2, hexane/AcOEt 85:15) gave **11b** (0.17 g, 60%). Brown liquid. $[\alpha]_D^{25} = -72.5$ ($c = 2.0$, $CHCl_3$). IR (neat): 2975, 1690, 1549, 1499, 1365, 1250, 1164. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.34–7.26 (*m*, 6 H); 6.34–6.30 (*m*, 2 H); 5.72 (*d*, $J = 7.3$, 1 H); 5.46 (*d*, $J = 8.3$, 1 H); 5.08 (*s*, 2 H); 4.64 (*s*, 1 H); 3.75 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 169.2; 155.4; 148.5; 142.8; 135.9; 128.5; 128.1; 126.9; 110.6; 108.6; 67.2; 53.0; 51.9. ESI-MS: 312 ($[M+Na]^+$). HR-ESI-MS: 312.0847 ($[M+Na]^+$, $C_{15}H_{15}NNaO_5^+$; calc. 312.0847).

Benzyl N*-{(1S)-2-{[(*tert*-Butyl)dimethylsilyl]oxy}-1-(furan-2-yl)ethyl}carbamate* (**12**). To the stirred soln. of **11b** (0.14 g, 0.5 mmol) in dry CH_2Cl_2 was added 1M DIBAL-H in toluene (1.5 ml) at −78° *via* syringe. The mixture was stirred for 1 h at −78° and for 2 h at −30°. Then, the reaction was quenched with MeOH (1 ml), the mixture extracted with AcOEt (3×10 ml), and the org. extract washed with 0.1N HCl (2×10 ml) and brine (2×10 ml), dried (Na_2SO_4), and concentrated to give crude primary alcohol (80%). To the primary alcohol (0.10 g, 0.4 mmol) in dry CH_2Cl_2 was added Et_3N (0.20 g, 0.8 mmol) followed by ^{t}BuMe$_2$SiCl (0.09 g, 0.6 mmol) at 0° successively. The mixture was stirred for 5 h at r.t. After 5 h, the solids were filtered through a *Celite* pad, and the resultant crude residue was purified by CC (SiO_2, hexane/AcOEt 8:2): **12** (0.11 g, 76%). Colorless oil. $[\alpha]_D^{25} = -14.1$ ($c = 2.0$, CH_2Cl_2) ([13c]: $[\alpha]_D^{25} = +13.1$ ($c = 1.15$, CH_2Cl_2)). IR (neat): 3452, 3331, 2929, 2856, 1725, 1499, 1249, 1134. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.38–7.28 (*m*, 6 H); 6.32 (*dd*, $J = 1.8, 3.5$, 1 H); 6.23 (*d*, $J = 3.4$, 1 H); 5.11 (*s*, 2 H);

5.04 (t, J = 3.9, 1 H); 4.82 (t, J = 6.0, 1 H); 3.51 (m, 1 H); 0.87 (s, 9 H); −0.05 (s, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 156.3; 154.4; 131.9; 136.5; 128.5; 128.1; 127.2; 110.1; 107.0; 67.3; 66.7; 46.1; 25.7; 18.1; −5.4. ESI-MS: 398 ($[M+Na]^+$). HR-MS: 398.1777 ($[M+Na]^+$, $C_{20}H_{29}NNaO_4Si^+$; calc. 398.1763).

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Received January 11, 2011