Preparation of Multiply Protected Alkylhydrazine Derivatives by Mitsunobu and PTC Approaches

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Keywords: Hydrazine derivatives / Phase-transfer catalysis / Mitsunobu reaction / α-Hydrazino acids / Protecting groups

Alkylation reactions of hydrazine derivatives by Mitsunobu or PTC approaches are described. It has been shown that aminophthalimide derivatives are better acidic partners than their aminoimidodicarbonate ($NBoc_2$) analogues, the presence of the phthaloyl group increasing the acidity of the sole proton and concomitantly reducing steric hindrance. Moreover, *N*-aminophthalimide derivatives can be efficiently converted into the corresponding *N*-amino-imidodicarbonates by a three-stage, one-flask procedure under very mild conditions. These procedures can also be efficiently used for the preparation of orthogonally N^{α},N^{β}-diprotected α-hydrazino esters.

Introduction

Phase-Transfer Catalysis (PTC) and the Mitsunobu reaction are the processes par excellence for the alkylation of various nucleophiles under mild reaction conditions. The Mitsunobu reaction is applicable for a wide range of primary and secondary alcohols and results in stereospecific alkylation.[1] However, there are disadvantages associated with the use of this procedure on a large scale. In particular, the by-products, triphenylphosphane oxide and dialkylhydrazinedicarboxylates, are of considerable mass, making the procedure far from ideal with regard to atom economy.[2] For this reason, phase-transfer catalysis alkylation is often preferred when non-chiral starting materials are used.[3] Ragnarsson and colleagues, for example, have recently shown that PTC and the Mitsunobu conditions constitute efficient synthetic routes for the preparation of substituted hydrazines. They demonstrated that multiply substituted hydrazines can be obtained from triprotected hydrazines by a PTC alkylation method.[3] However, although primary and benzylic groups can be easily introduced, hydrazines substituted with secondary alkyl group cannot be obtained in this way.

In order to investigate the utility of PTC and Mitsunobu methods for the alkylation of hydrazine derivatives further, we have compared them for the preparation of the *N*-acyl and *N*-(alkyloxycarbonyl)aminophthalimides **2**. As part of an effort to develop new synthetic approaches for the preparation of protected hydrazines, we had previously demonstrated that *N*-acyl and *N*-[(alkyloxycarbonyl)amino]-phthalimides can be used as acidic partners in the Mitsunobu reaction, with our work showing that N^{β},N^{β},-disubstituted hydrazines could be efficiently prepared after removal of the protecting groups.[4a] In that study, both primary and, more interestingly, secondary alkyl groups, as well as functionalized groups, were introducible with good overall yields.[4] It is important, however, to recognize that the use of the phthaloyl group can sometimes be regarded as a drawback as it is often difficult to remove this protecting group under mild conditions. In order to address this potential problem, in the studies presented here we have also examined the possibility of using iminodicarbonate derivatives ($NBoc_2$) **5** as acidic partners in alkylation processes. Finally, we demonstrate that the phthaloyl group can be converted into Boc protection in a "one-flask" reaction procedure.[5]

Results and Discussion

Synthesis of Starting Materials

The results for the preparation of compounds **2** and **5**, reported in Scheme 1, show that the range of compounds prepared by the PTC and Mitsunobu methods can be expanded and that the strategies selected can be optimized in relation to what we had previously described.[4a,6] Compounds **2** were obtained by condensation of the commercially available carbamates (**1**: R = O*t*Bu or OCH_2Ph) or hydrazides [**1**: R = CH_3, C_6H_5, $CH_3(CH_2)_6$, $ZNHCH_2$, $ZNHCH(CH_3)$] with phthalic anhydride in toluene at reflux. The compounds **5** were prepared in good yields in three steps, involving: a) protection of the NH group of **2** R = O*t*Bu with Boc_2O/DMAP, b) a dephthaloylation reaction resulting in the formation of N^{β},N^{β}-bis(*tert*-butoxycarbonyl)hydrazine (**4**), and c) acylation of **4** with carbonyldiimidazole as a coupling reagent.[6]

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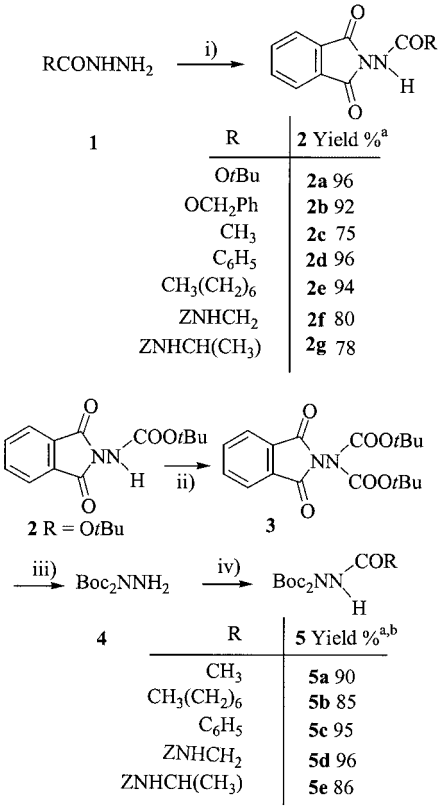
 DOI: 10.1002/ejoc.200300445

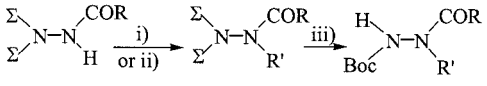


i) Phthalic anhydride, toluene ii) Boc_2O, DMAP cat.(80%) iii) NH_2NH_2, EtOH, -20°C (87%) iv) RCOOH, $COIm_2$, THF a) yield of isolated compounds b)calculated from **4**

Scheme 1

Alkylation Reactions

Scheme 2 and the associated Table 1 show the results obtained by the Mitsunobu approach (Method A) and under PTC conditions (Method B).



2 Σ, Σ = phthaloyl **6** Σ, Σ = phthaloyl **10**
5 Σ = Boc **7** Σ = Boc

i) *Method A* : R'OH 1.2 equiv., DIAD 1.2 equiv., PPh_3 1.2 eq., THF, r.t., 0.5 h
ii) *Method B* : CH_3I or R'Br 1.2 equiv., K_2CO_3, $BnEt_3NCl$, MeCN, 50°C
iii) $Mg(ClO_4)_2$ catalytic, CH_3CN

Scheme 2

Mitsunobu Conditions (Method A): We employed the conditions previously described, with the use of a slight excess of alcohol (R′OH), triphenylphosphane and DIAD in THF at room temperature.[4a]

Phase-Transfer Catalyst Conditions (Method B): Acidic partners **2** or **5** were alkylated with alkyl bromide R′Br or CH_3I under phase-transfer catalysis conditions in acetonitrile at 50 °C in the presence of potassium carbonate as base and an ammonium salt ($BnEt_3NCl$) as catalyst according to a procedure described in the literature.[3a] A systematic study, not reported in this paper, showed that the nature of the ammonium salt has very little effect on the yield of the reaction but a significant effect on the reaction time (from 20 h for $BnEt_3NCl$ to 100 h for Bu_4NI).

Alkylation with Primary Alkyl Groups

When starting from compounds **2**, primary alkyl groups can be introduced by use either of Mitsunobu (method A) or PTC (method B) conditions to give compounds **6** in good to excellent yields.

However, the alkylation of the compounds **5a** and **5b** (for which R = alkyl) by the Mitsunobu approach failed. It is interesting, though, to note that this kind of alkylation did become possible when acidic partners **5d** and **5e**, containing electron-withdrawing groups, were used. This led us to postulate that electronic effects are an important factor governing the reaction. No such effects were observed when PTC conditions were used: incorporation of primary alkyl groups could be performed in good to excellent yields regardless of the nature of the starting materials.

Alkylation with Secondary Alkyl Groups

In contrast with the PTC alkylation of triprotected hydrazines previously described in the literature,[3] PTC alkylation of *N*-aminopththalimide derivatives **2** with secondary alkyl groups can be performed in good yields, so alkylation of **2b** in comparable yields can be achieved under either Mitsunobu or PTC conditions. When applied to the more hindered *N*-[(*tert*-butoxycarbonyl)amino]phthalimide (**2a**), PTC conditions gave yields of the corresponding compounds **6** 20 % lower than had been obtained by the Mitsunobu procedure. As suggested before,[4a] the success of these reactions depends mainly on the presence of the phthaloyl moiety, in which two acyl groups are incorporated into a ring, which reduces steric hindrance. In fact, all attempts to alkylate the sterically hindered imidodicarbonate derivatives (compounds **5**) with secondary alkyl groups failed either by method A or by method B (unreported results).

Moreover, the introduction of secondary alkyl groups onto the acidic partner, particularly onto **2a**, gives better yields when the Mitsunobu approach is involved, suggesting that PTC alkylation is more sensitive to steric hindrance than the Mitsunobu reaction. In the synthesis of chiral hydrazine derivatives, we have previously demonstrated that the conversion of chiral α-hydroxy esters into hydrazine derivatives by the Mitsunobu reaction occurred with a complete inversion of the configuration and was accompanied with a negligible loss of the enantiomeric purity (determined by HPLC after conversion into amino acid and derivatisation).[4b] In contrast, this study showed that, when starting from (*S*)-bromopropanoate derivatives, the use of PTC conditions afforded the corresponding α-hydrazino esters **6q** or **6t** with total loss of optical purity ($[\alpha]_D = 0$). This racemization could be explained by an enolisation of

Table 1. Preparation of the alkylhydrazine derivatives **6**, **7**, **10**

2 or **5**	R	R′		**2** → **6** or **5** → **7** Method A % yield[a]	Method B % yield[a] (time)	**6** → **7** % Yield[a]	**7** → **10** % Yield[a]
2a	O*t*Bu	CH_3	**6a**	97[b]	71[c] (12 h)	**7k**: 82	**10k**: 96
2a	O*t*Bu	CH_2Ph	**6b**	83[b]	96 (2 h)	**7l**: 91	**10l**: 84
2a	O*t*Bu	$(CH_2)_5CH_3$	**6c**	86[b]	91 (24 h)		
2a	O*t*Bu	$CH_2CH=CH_2$	**6d**	67[b]	85 (18 h)		
2a	O*t*Bu	CH_2COOCH_3	**6e**	70	86 (2 h)		
2b	OBzl	CH_3	**6f**	94[b]	94[c] (12 h)	**7o**: 76	**10o**: 98
2b	OBzl	CH_2Ph	**6g**	84[b]	92 (2 h)	**7p**: 80	**10p**: 96
2b	OBzl	$(CH_2)_5CH_3$	**6h**	80	87 (3 h)		
2b	OBzl	$CH_2CH=CH_2$	**6i**	86	82 (1 h)		
2b	OBzl	CH_2COOCH_3	**6j**	81[d]	78 (4 h)		
2c	CH_3	CH_3	**6k**	85	89 (24 h)	**7a**: 90	**10a**: 85
2c	CH_3	CH_2Ph	**6l**	80	82 (5 h)	**7b**: 94	**10b**: 81
2d	C_6H_5	CH_3	**6m**	90	92 (15 h)	**7e**: 75	**10e**: 86
2d	C_6H_5	CH_2Ph	**6n**	85	86 (16 h)	**7f**: 80	**10f**: 85
5a	CH_3	CH_3	**7a**	0	58 (48 h)		
5a	CH_3	CH_2Ph	**7b**	0	81 (48 h)		
5b	$(CH_2)_6CH_3$	CH_3	**7c**	0	43 (48 h)		
5b	$(CH_2)_6CH_3$	CH_2Ph	**7d**	0	92 (48 h)		
5c	Ph	CH_3	**7e**	42	69 (24 h)		
5c	Ph	CH_2Ph	**7f**	60	54 (2 h)		
5d	$ZNHCH_2$	CH_3	**7g**	77	70 (24 h)		
5d	$ZNHCH_2$	CH_2Ph	**7h**	40	83 (2 h)		
5e	ZNHCH(Me)	CH_3	**7i**	50	68 (24 h)		
5e	ZNHCH(Me)	CH_2Ph	**7j**	35	84 (2 h)		
2a	O*t*Bu	$CH(CH_3)_2$	**6o**	77[b]	46[d](150 h)		
2a	O*t*Bu	Cyclopentyl	**6p**	85[b]	49 (15 h)	**7m**: 92	**10m**: 95
2a	O*t*Bu	(*S*)$CH(CH_3)COOMe$	**6q**	82[d]	70 (30 h)	**7n**: 84	**10n**: 97
2b	OBzl	$CH(CH_3)_2$	**6r**	61	75[d](150 h)		
2b	OBzl	Cyclopentyl	**6s**	83	71 (10 h)	**7q**: 76	**10q**: 91
2b	OBzl	(*S*)$CH(CH_3)COOEt$	**6t**	90[d]	93 (2 h)	**7r**: 90	**10r**: 90
2e	$(CH_2)_6CH_3$	CH_3	**6u**	74		**7c**: 86	**10c**: 86
2e	$(CH_2)_6CH_3$	CH_2Ph	**6v**	79		**7d**: 72	**10d**: 83
2f	$ZNHCH_2$	CH_3	**6w**	88		**7g**: 84	**10g**: 91
2f	$ZNHCH_2$	CH_2Ph	**6x**	82		**7h**: 78	**10h**: 91
2g	ZNHCH(Me)	CH_3	**6y**	93[b]		**7i**:[e] 94	**10i**: 93
2g	ZNHCH(Me)	CH_2Ph	**6z**	97[b]		**7j**: 81	**10j**: 77

[a] Yield of isolated compounds. [b] See reference.[4a] [c] For volatile reagents, reactions were performed at room temperature with 4 equiv. of alkyl halides. [d] See reference.[4b] [e] Including 29 % of compound **7i′** $BocZNCH(CH_3)CONMeNBoc_2$.

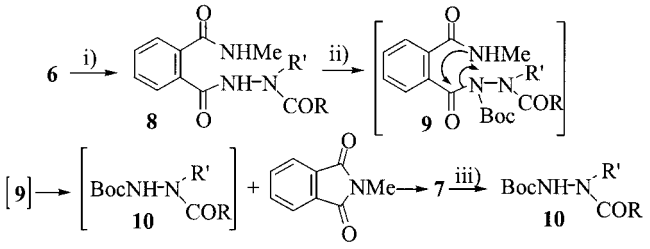
the alkyl halide prior to the substitution reaction in the medium.

To summarise, compounds **2** can be efficiently alkylated by primary or secondary alkyl groups either by the PTC or by the Mitsunobu approach and are better acidic partners than imidodicarbonate analogues **5**. These results can be explained by the presence of the phthaloyl group, which contributes to an increase in the acidity of the sole proton and concomitantly to a reduction in the steric hindrance. Unfortunately, as other authors have reported, we were confronted with the difficulty involved in finding general mild conditions for removal of the phthaloyl group. In some cases this drawback contributed to the detriment of this new strategy of hydrazine derivatives synthesis. In order to find mild efficient conditions to remove the phthaloyl group and to obtain Boc protection of our hydrazine derivatives, we developed a strategy to transform a phthaloyl moiety into a Boc group.

Transprotection Reaction

In preliminary studies[5] we showed that the use of methylamine, described in the literature for the dephthaloylation of some protected amines,[7] was not efficient for removal of the phthaloyl group in compounds **6**. These conditions actually resulted in the formation of compounds **8**, products of opening of the phthaloyl ring. From this observation, we deduced that the attachment of an electron-withdrawing group onto the acidic nitrogen atom of the hydrazide function might help the dephthaloylation step by favouring the splitting of the CO−N bond of the hydrazide group.[8] This strategy has been reported in the literature previously, since amides can be activated towards hydrolysis by prior conversion into the *N*-Boc imide derivatives. As a result, we were able to show that the removal of the phthaloyl group of **8** can be achieved very efficiently by the use of $(Boc)_2O$ in the presence of a catalytic amount of

DMAP. In fact, use of these conditions resulted in the direct formation of the corresponding N^{β},N^{β}-bis(*tert*-butoxycarbonyl)hydrazides or carbazates **7**. Systematic assays performed on compound **6g** demonstrated that the reaction was better achieved with 3 equivalents of $(Boc)_2O$, since the use of one equivalent of reagent resulted in the formation of a mixture of compounds **7p** and **10p** (in 25 % and 55 % yields, respectively). To improve our technique, we carried out investigations to perform the conversion of phthaloylhydrazides or carbazates **6** into the corresponding compounds **7** in a one-flask fashion that might potentially find use in the combinatorial synthesis of Boc-protected hydrazides or carbazates. The results reported in the Table 1 (**6** → **7**) show that the conversions of **6** into **7** occurred in very good yields, regardless of the nature of R or R′ (R′ can also be a secondary group). Moreover, we also demonstrated on a few examples that this strategy can be applied for the preparation of orthogonal N^{α},N^{β}-triprotected α-hydrazino esters (see compounds **7g**−**7j**). A proposed mechanism of formation of **7** is given in Scheme 3.

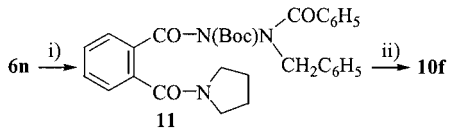


i) $MeNH_2$, THF ii) Boc_2O, DMAP cat., THF iii) $Mg(ClO_4)_2$ cat. DMF

Scheme 3

As described above, the action of the methylamine on **6** gave the corresponding compound **8**, which can be isolated. The mechanism then predicts a selective reaction between $(Boc)_2O$ and the nitrogen of the hydrazide group of **8**, affording the non-isolable compound **9**. The cleavage of the C−N bond in the hydrazide moiety can be explained in terms of an intramolecular attack of the nitrogen atom of the amide group. The isolation and the identification of the methylphthalimide as a by-product of the reaction is in agreement with the proposed reaction mechanism. The formation of compound **7** would be the result of the reaction of a second equivalent of $(Boc)_2O$. On one example we demonstrated that the replacement of the methylamine in step i) by a secondary amine allowed the isolation of compound **11** from **6n**; the conversion of **11** to **10f** then required the use of another nucleophile − methylamine − in step ii) (Scheme 4). This result is in agreement with the proposed reaction mechanism.

Finally, we showed that the presence of a catalytic amount of $Mg(ClO_4)_2$ in CH_3CN[9] promoted mild, selective monodeprotection of imidodicarbonates **7** to yield compounds **10** (Scheme 3, Table 1, **7** → **10**).



i) 1) pyrolidine 1.5 equiv., THF, r.t., 72h 2) Boc_2O, DMAP cat., THF, r.t., 87% ii) $MeNH_2$, THF, r.t., 10mn, 100%

Scheme 4

Conclusion

Protected alkylhydrazines can be obtained by alkylation of the phthalimide derivatives **2**. Thanks to the particular structural features pertaining when the two acyl groups are incorporated into a ring, these compounds have been shown to be better acid partners than imidodicarbonate analogues **5** in Mitsunobu and PTC procedures, allowing their alkylation by either primary or secondary groups. The obtained *N*-aminophthalimide derivatives **6** can be efficiently converted into the corresponding *N*-(amino)imidodicarbonates **7** under very mild conditions by use of a three-stage, one-flask method. Selective removal of one Boc group of compounds **7** resulted in the formation of *N*-(*tert*-butoxycarbonyl)hydrazine derivatives **10**. This strategy can also be applied for the preparation of orthogonally N^{α},N^{β}-diprotected α-hydrazino esters.

Experimental Section

General: Melting points were obtained on a hot-stage apparatus and were uncorrected. NMR spectra were recorded with spectrometers operating at 400 MHz or 250 MHz. Mass spectra were performed by the ULIRS Mass Spectrometry Facility (the School of Pharmacy, London). Tetrahydrofuran were dried by distillation over sodium-benzophenone.

General Procedure for the Preparation of *N*-Acyl- and *N*-[(Alkyloxycarbonyl)amino]phthalimides 2: Hydrazide or carbazate (0.1 mol) was added to a suspension of phthalic anhydride (0.1 mol, 14.8 g) in toluene (200 mL) and the resulting mixture was heated to reflux, the water formed in the reaction being trapped in a Dean−Stark receiver. After 3 h, the solution was cooled to 0 °C; after filtration, the solid obtained by precipitation was recrystallised from EtOAc/hexane (or $CHCl_3/CCl_4$ for **2b**). Spectroscopic data of compounds **2a**−**d** were previously described.[4a]

***N*$^{\alpha}$-[(Heptanoyl)amino]phthalimide (2e):** M.p. 103 °C. IR (KBr): $\tilde{\nu}$ = 3273, 1799, 1750, 1665 cm−1. ^{1}H NMR ($CDCl_3$): δ = 8.64 (s, 1 H), 7.86−7.62 (m, 4 H), 2.45−2.25 (m, 2 H), 1.74−1.49 (m, 2 H), 1.40−1.11 (m, 8 H), 0.95−0.72 (m, 3 H) ppm. ^{13}C NMR: δ = 173.0, 165.7, 135.0, 130.3, 124.2, 34.1, 32.0, 29.4, 25.7, 23.0, 14.4 ppm.

***N*′-(Benzyloxycarbonyl)-*N*$^{\beta}$-phthaloylglycinehydrazide (2f):** M.p. 155 °C. IR (KBr): $\tilde{\nu}$ = 3346, 3197, 1794, 1764, 1741, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 12.00 and 11.02 (m, 1 H), 10.11−9.92 (m, 1 H), 8.32−7.74 (m, 4 H), 7.56−7.01 (m, 5 H), 5.04 (s, 2 H), 3.82 (d, *J* = 7.2 Hz, 2 H) ppm. ^{13}C NMR: δ = 168.8, 164.3, 157.3, 137.8,

133.4, 129.2, 128.6, 128.5, 125.9, 66.4, 42.8 ppm. $C_{18}H_{15}N_3O_5$ (353.3): calcd. C 61.19, H 4.28, N 11.89; found C 61.21, H 4.34, N 11.88.

Procedure for the Preparation of N^{β},N^{β}-Bis(*tert*-butoxycarbonyl)-hydrazine (4): A solution of *N*-[(*tert*-butoxycarbonyl)amino]phthalimide (**2**) R = O*t*Bu (20 mmol, 5.2 g), Et_3N (5 mL) and a catalytic amount of DMAP in THF (150 mL) was stirred and cooled in an ice-water bath. Di-(*tert*-butyl) dicarbonate (6.5 g, 30 mmol) was added and stirring was continued at room temperature for 15 min. The solution was concentrated in vacuo. Water and diethyl ether were added, and the aqueous layer was separated and extracted twice with diethyl ether. The organic layer was washed with diluted HCl and dried with $MgSO_4$, and the solvents were evaporated to dryness. The residue was chromatographed through silica gel with EtOAc/hexane to give N^{β},N^{β}-[bis(*tert*-butoxycarbonyl)amino]phthalimide (**3**) (80 %). $H_2N-NH_2{\cdot}H_2O$ (1.5 equivalents, 0.750 mL) was then added by syringe at −20 °C to a suspension of **3** (10 mmol, 3.62 g) in EtOH (100 mL). The solution was warmed to room temperature, and after 15 min a white precipitate was filtered off. The filtrate was evaporated to give a solid, which was chromatographed through silica gel with EtOAc/hexane to give pure compound **4** (87 %).

General Procedure for the Preparation of N^{β},N^{β}-Bis(*tert*-butyloxycarbonyl)hydrazines 5: 1,1′-Carbonyldiimidazole (10 mmol, 1.62 g) was added to a solution of carboxylic acid (10 mmol) in THF. The mixture was heated at reflux for 10 min (corresponding to the end of CO_2 evolution), and N^{β},N^{β}-bis(*tert*-butyloxycarbonyl)hydrazine (**4**) (5 mmol, 1.16 g) was then added. Heating at reflux was continued for 20−96 h (monitored by TLC until completion). The medium was concentrated in vacuo and the residue was partitioned between water and diethyl ether. The water layer was extracted twice with diethyl ether, the organic layer was dried with $MgSO_4$ and concentrated in vacuo, and the residue was chromatographed on silica gel.

N^{α}-Acetyl-N^{β},N^{β}-bis(*tert*-butyloxycarbonyl)hydrazine (5a): Yield 90 %; m.p. 109 °C. IR (KBr): $\tilde{\nu}$ = 3302, 1759, 1675 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.47 (s, 1 H), 1.98 (s, 3 H), 1.47, 1.43 (2 s, 18 H) ppm. ^{13}C NMR: δ = 169.2, 151.1, 84.1, 28.2, 20.8 ppm. $C_{12}H_{22}N_2O_5$ (274.3): calcd. C 52.54, H 8.08, N 10.21; found C 52.06, H 7.84, N 10.34.

N^{β},N^{β}-Bis(*tert*-butyloxycarbonyl)-N^{α}-heptanoylhydrazine (5b): Yield 85 %; m.p. 78 °C. IR (KBr): $\tilde{\nu}$ = 3310, 1774, 1677 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.54 (s, 1 H), 2.16 (t, *J* = 7.5 Hz, 2 H), 1.62−1.50 (m, 2 H), 1.37 (s, 18 H), 1.28−1.10 (m, 8 H), 0.76 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR: δ = 172.0, 150.9, 83.6, 34.1, 31.9, 29.5, 23.3, 28.1, 25.6, 22.8, 14.3 ppm. $C_{18}H_{26}N_2O_5$: calcd. C 60.31, H 9.56, N 7.81; found C 60.28, H 9.46, N 7.90.

N^{α}-Benzoyl-N^{β},N^{β}-bis(*tert*-butyloxycarbonyl)hydrazine (5c): Yield 95 %; m.p. 172 °C. IR (KBr): $\tilde{\nu}$ = 3313, 1766, 1692 cm^{-1}. ^1H NMR (DMSO): δ = 10.86 (s, 1 H), 7.86 (s, 2 H), 7.59−7.41 (m, 3 H), 1.41 (s, 18 H) ppm. ^{13}C NMR: δ = 165.4, 150.5, 132.3, 132.0, 128.6, 127.5, 82.8, 27.7 ppm. $C_{17}H_{24}N_5O_2$ (330.4): calcd. C 60.70, H 7.19, N 8.33; found C 60.62, H 7.19, N 8.42.

N'-(Benzyloxycarbonyl)-N^{β},N^{β}-bis(*tert*-butyloxycarbonyl)glycine-hydrazide (5d): Yield 96 %. IR (neat): $\tilde{\nu}$ = 3299 1760, 1718 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 9.15 (s, 1 H), 7.29−7.17 (m, 5 H), 6.18−6.11 (pt, 1 H), 5.01 (m, 2 H), 3.91 (d, *J* = 5 Hz,2 H,), 1.45, 1.40 (2s, 18 H) ppm. ^{13}C NMR: δ = 168.6, 157.2, 150.8, 136.6, 128.8, 128.4, 128.3, 84.2, 67.3, 28.2 ppm. HRMS calcd. for $C_{20}H_{33}N_4O_7$ [M + NH_4^+] *m*/*z* = 441.2349 found 441.2339.

(*S*)-N'-(Benzyloxycarbonyl)-N^{β},N^{β}-bis(*tert*-butyloxycarbonyl)-alaninehydrazide (5e): Yield 86 %; m.p. 138−140 °C. IR (KBr): $\tilde{\nu}$ = 3264, 1763, 1703 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 9.25 and 9.18 (2 s, 1 H), 7.32−7.21 (m, 5 H), 6.06 and 6.02 (2 d, 1 H), 5.06−4.98 (m, 2 H), 4.46−4.35 (m, 1 H), 1.52−1.34 (m with s at 1.45, 21 H) ppm. ^{13}C NMR: δ = 171.0, 156.5, 150.7, 136.4, 128.9, 128.6, 128.4, 84.3, 67.4, 49.2, 28.3, 18.6 ppm. $C_{21}H_{31}N_3O_7$ (437.5): calcd. C 57.65, H 7.14, N 9.60; found C 57.57, H 7.15, N 9.77.

General Procedure for the Alkylation with Alcohols (Mitsunobu's Procedure. Method A): DIAD (7.5 mmol, 1.5 g) was added in one portion with stirring under nitrogen at 0−5 °C to a solution of **2** or **5** (5 mmol), PPh_3 (7.5 mmol, 2 g) and alcohol (R-OH, 7.5 mmol) in dry THF. The resulting solution was stirred at room temperature for 0.5 h (monitored by TLC until completion) and concentrated in vacuo. The residue was evaporated and the residue was chromatographed on silica gel (with a mixture of hexane and EtOAc as eluent).

General Procedure for the Alkylation with Alkyl Halides (PTC Procedure, Method B): Dry K_2CO_3 (7.6 mmol, 4 equiv.) and $BnEt_3NCl$ (0.2 equiv.) were added to a solution of **2** or **5** (1.9 mmol) in MeCN (8 mL). The alkyl halide (CH_3I or R′Br, 1.25 or 4 equiv.; see Table 1) was added dropwise (over 5 min) under nitrogen and the resulting mixture was vigorously stirred at the temperature and for the time indicated in the Table 1 (monitored by TLC until completion). Water (50 mL) was added and the mixture was extracted three times with diethyl ether. The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (with a mixture of hexane and EtOAc as eluent). Spectroscopic data of compounds **6a**−**g**, **j**−**q**, **t**, **y**, **z** were previously described.[4a]

***N*-[(Benzyloxycarbonyl)(hexyl)amino]phthalimide (6h):** IR (NaCl): $\tilde{\nu}_{max.}$ = 1796, 1746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.90−7.68 (m, 4 H), 7.41−7.09 (m, 5 H), 5.23 and 5.10 (2 s, 2 H), 3.80−3.69 (m, 2 H), 1.67−1.17 (m, 8 H), 0.85 (t, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 165.8, 165.5, 154.9, 154.7, 136.1, 135.9, 135.2, 135.1, 130.2, 130.1, 128.9, 128.7, 128.4, 128.3, 127.5, 124.2, 69.0, 68.4, 51.1, 50.4, 31.8, 28.4, 28.0, 26.5, 22.9, 14.4 ppm. HRMS calcd. for $C_{22}H_{24}N_2O_4$ [M^+] *m*/*z* = 380.1736 found 380.1723.

***N*-[(Allyl)(benzyloxycarbonyl)amino]phthalimide (6i):** IR (NaCl): $\tilde{\nu}_{max}$ = 1796, 1740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.89−7.65 (m, 4 H), 7.43−7.02 (m, 5 H), 6.00−5.80 (m, 1 H), 5.23−5.03 (m, 2 H), 4.31−4.19 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ = 165.0 and 164.7, 154.1, 135.5 and 135.4, 134.8, 131.8 and 131.7, 129.5 and 129.4, 128.5, 128.3, 127.9, 127.1, 123.7, 119.8, 68.6, 68.1, 53.3, 52.3 ppm. HRMS calcd. for $C_{19}H_{16}N_2O_4$ [M^+] *m*/*z* = 336.1742 found 336.1743.

***N*-[(Benzyloxycarbonyl)(isopropyl)amino]phthalimide (6r):** IR (NaCl): $\tilde{\nu}_{max.}$ = 1794, 1745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.95−7.88 (m, 4 H), 7.45−7.07 (m, 5 H), 5.25 and 5.11 (2 s, 2 H), 4.71 and 4.58 (2 hept., 1 H), 1.26 (d, *J* = 6.5 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 166.9, 166.5, 153.9, 136.2, 136.0, 135.2, 130.4, 130.2, 129.0, 128.7, 128.5, 128.4, 128.3, 127.4, 124.3, 69.0, 68.2, 60.7, 52.2, 51.5, 21.2, 20.8, 14.6 ppm. HRMS calcd. for $C_{19}H_{22}N_3O_4$ [M + NH_4^+] *m*/*z* = 356.1610 found 356.1610.

***N*-[(Benzyloxycarbonyl)(cyclopentyl)amino]phthalimide (6s):** IR (NaCl): $\tilde{\nu}_{max}$ = 1796, 1740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.85−7.82, 7.72−7.66 (m, 4 H), 7.37−7.02 (m, 5 H), 5.19 and 5.06 (2 s, 2 H), 4.81−4.59 (m, 1 H), 2.06−1.93 (m, 4 H), 1.74−1.42 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 166.6, 166.3, 154.3, 136.1, 135.3, 130.1, 128.9, 128.7, 128.2, 127.3, 124.3, 69.0, 68.3, 61.3, 60.8,

30.6, 30.0, 23.6 ppm. HRMS calcd. for $C_{21}H_{24}N_3O_4$ [M + NH_4^+] *m*/*z* = 382.1767 found 383.1772.

***N*-[(Methyl)(heptanoyl)amino]phthalimide (6u):** M.p. 68 °C. IR (KBr): ṽ = 1795, 1736, 1623 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.97−7.65 (m, 4 H), 3.40 and 3.18 (2 s, 3 H), 2.47 and 2.04 (2 t, 2 H, *J* = 7.5 Hz), 1.69−1.44 (m, 2 H), 1.37−1.04 (m, 8 H), 0.83−0.69 (m, 3 H) ppm. ^{13}C NMR: δ = 174.6, 171.9, 165.4, 164.9, 135.6, 134.9, 130.4, 130.0, 124.5, 124.2, 38.9, 35.4, 33.1, 32.0, 31.9, 31.7, 29.4, 29.3, 29.2, 24.9, 24.6, 22.9, 22.8, 14.3 ppm. $C_{17}H_{22}N_2O_3$ (302.4): calcd. C 67.53, H 7.33, N 9.26; found C 67.42, H 7.30, N 9.30.

***N*-[(Benzyl)(heptanoyl)amino]phthalimide (6v)**: M.p. 72 °C. IR (KBr): ṽ = 1815, 1735, 1690 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.92−7.67 (m, 4 H), 7.55−7.13 (m, 5 H), 4.98 and 4.94 (2 s, 2 H), 2.58 and 2.16 (2 t, *J* = 7.5 Hz, 2 H), 1.78−1.57 (m, 2 H), 1.43−1.15 (m, 8 H), 0.91−0.80 (m, 3 H) ppm. ^{13}C NMR: δ = 174.6, 165.1, 135.4, 134.9, 134.7, 130.0, 129.6, 129.1, 128.7, 128.6, 128.5, 128.3, 124.4, 124.2, 55.1, 51.4, 32.4, 32.0, 29.4, 24.7, 22.9, 14.4 ppm. $C_{23}H_{26}N_2O_3$ (378.5): calcd. C 72.99, H 6.93, N 7.40; found C 72.67, H 7.06, N 7.40.

***N*′-(Benzyloxycarbonyl)-N^{α}-methyl-N^{β}-(phthaloyl)glycinehydrazide (6w):** M.p. 149 °C. IR (KBr): ṽ = 3328, 1792, 1747, 1684 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.97−7.76 (m, 4 H), 7.36−7.26 (m, 5 H), 5.72−5.62 (m, 1 H), 5.12 and 5.05 (2 s, 2 H), 4.29 and 3.89 (2 d, *J* = 4.5 Hz, 2 H), 3.41 and 3.29 (2 s, 3 H) ppm. ^{13}C NMR: δ = 170.2, 164.6, 156.3, 136.7, 135.8, 135.3, 130.0, 128.9, 128.5, 128.4, 124.8, 124.5, 67.4, 42.3, 35.8 ppm. $C_{19}H_{17}N_5O_3$ (363.4): calcd. C 62.12, H 4.66, N 11.44; found C 62.03, H 4.70, N 11.52.

***N*-Benzyl-*N*′-(benzyloxycarbonyl)-N^{β}-(phthaloyl)glycinehydrazide (6x):** M.p. 132 °C. IR (KBr): ṽ = 3364, 1796, 1735, 1713, 1686 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.92−7.70 (m, 4 H), 7.49−7.11 (m, 10 H), 5.77−5.62 (m, 1 H), 5.20−4.84 (m, 4 H), 4.05−3.82 (m, 2 H) ppm. ^{13}C NMR: δ = 170.2, 164.7, 156.4, 136.7, 135.6, 133.6, 130.2, 129.5, 129.2, 128.9, 128.7, 128.5, 128.4, 124.6, 124.4, 67.4, 52.0, 42.8 ppm. $C_{25}H_{21}N_3O_5$ (443.5): calcd. C 67.71, H 4.77, N 9.47; found C 67.47, H 4.80, N 9.49.

General Procedure for the Transprotection Reaction: A solution of methylamine (4.5 mM, 2 M in MeOH) was added at room temperature to a solution of compound **6** (3 mM) in THF (20 mL). The mixture was stirred at room temperature until completion (1 to 4 h, monitored by TLC). The solvent and the excess of methylamine were removed in vacuo. The residue was dissolved in THF (20 mL), and Boc_2O (9 mM, 2 g) and a catalytic amount of DMAP were added. The mixture was stirred at room temperature until completion (1 to 4 h, monitored by TLC). The solvent was removed in vacuo and the residue was separated by column chromatography.

N^{α}-Acetyl-N^{β},N^{β}-bis(*tert*-butyloxycarbonyl)-N^{α}-methylhydrazine (7a): M.p. 80 °C. IR (KBr): ṽ = 1754, 1710, 1699 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.06 (s, 3 H), 1.93 (s, 3 H), 1.50 (s, 18 H) ppm. ^{13}C NMR: δ = 172.4, 150.0, 84.9, 34.9, 28.3, 20.2 ppm. $C_{13}H_{24}N_2O_5$ (288.3): calcd. C 54.15, H 8.39, N 9.71; found C 54.22, H 8.40, N 9.75.

N^{β}-(Acetyl)-N^{α}-benzyl-N^{β}-bis(*tert*-butyloxycarbonyl)hydrazine (7b): M.p. 70−75 °C. IR (KBr): ṽ = 1757, 1726, 1679 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.27−7.16 (m, 5 H), 4.61 (s, 2 H), 1.91 (s, 3 H), 1.27 (s, 18 H) ppm. ^{13}C NMR: δ = 172.6, 150.0, 135.3, 130.7, 128.7, 128.2, 54.6, 51.4, 28.1, 20.5 ppm. $C_{19}H_{28}N_2O_5$ (364.4): calcd. C 62.62, H 7.74, N 7.69; found C 63.25, H 6.68, N 8.10.

N^{β},N^{β}-Bis(*tert*-butyloxycarbonyl)-N^{α}-heptanoyl-N^{α}-methylhydrazine (7c): IR (neat): ṽ = 1802, 1764, 1724, 1666 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.01 (s, 3 H), 2.25 and 2.07 (2 t, *J* = 7.3 Hz, 2 H), 1.65−1.11 (m with s at 1.14, 28 H), 0.84−0.74 (m, 3 H) ppm. ^{13}C NMR: δ = 174.7, 150.1, 84.7, 34.9, 32.0, 31.6, 29.7, 29.3, 28.2, 24.8, 22.9, 14.3 ppm. HRMS calcd. for $C_{19}H_{37}N_2O_5$ [M + H^+] *m*/*z* = 373.2702, found 373.2694.

N^{α}-Benzyl-N^{β},N^{β}-bis(*tert*-butyloxycarbonyl)-N^{α}-heptanoylhydrazine (7d): IR (neat): ṽ = 3088, 3064, 3030, 1801, 1765, 1731, 1686 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.31−7.21 (m, 5 H), 4.66 (s, 2 H), 2.42 and 2.14 (2 t, *J* = 7.3 Hz, 2 H), 1.60 and 1.57 (m, 2 H), 1.41−1.17 (m with s at 1.30, 26 H), 0.87−0.79 (m, 3 H) ppm. ^{13}C NMR: δ = 174.6, 150.0, 135.4, 130.6, 128.5, 128.0, 84.1, 51.4, 31.8, 31.7, 29.5, 29.2, 27.9, 24.5, 22.7, 14.2 ppm. HRMS calcd. for $C_{25}H_{40}N_2O_5$ *m*/*z* = 448.2937, found 448.2935.

N^{α}-Benzoyl-N^{β},N^{β}-bis(*tert*-butyloxycarbonyl)-N^{α}-methylhydrazine (7e): M.p. 58−60 °C. IR (KBr): ṽ = 1754, 1717, 1677 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.32−7.10 (m, 5 H), 3.06 (s, 3 H), 1.36 and 1.25 (2 s, 18 H) ppm. ^{13}C NMR: δ = 172.7, 149.9, 134.8, 130.7, 128.2, 126.8, 84.6, 35.5, 28.1 ppm.

N^{α}-Benzoyl-N^{α}-benzyl-N^{β},N^{β}-bis(*tert*-butyloxycarbonyl)hydrazine (7f): M.p. 99 °C. IR (KBr): ṽ = 1798, 1661 ppm. ^1H NMR ($CDCl_3$): δ = 7.57−7.22 (m, 10 H), 4.89 (s, 2 H), 1.43 and 1.29 (2s, 18 H) ppm. ^{13}C NMR: δ = 172.8, 135.2, 135.1, 131.1, 130.7, 128.8, 128.6, 128.3, 128.2, 84.7, 52.6, 28.2 ppm. $C_{24}H_{30}N_2O_5$ (426.5): calcd. C 67.59, H 7.09, N 6.57; found C 67.79, H 7.14, N 6.71.

***N*′-(Benzyloxycarbonyl)-N^{β},N^{β}-bis(*tert*-butyloxycarbonyl)-N^{α}-methylglycinehydrazide (7g):** IR (KBr): ṽ = 1802, 1765, 1724, 1702 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.38−7.27 (m, 5 H), 5.60−5.54 (m, 1 H), 5.11 (s, 2 H), 3.89 (d, *J* = 4.6 Hz, 2 H), 3.13 (s, 3 H), 1.53 (s, 18 H) ppm. ^{13}C NMR: δ = 170.4, 156.5, 149.7, 136.8, 128.6, 128.2, 85.3, 66.9, 42.1, 35.0, 28.0 ppm. HRMS calcd. for $C_{21}H_{32}N_3O_7$ [M + H^+] *m*/*z* = 438.2240 found 438.2256.

N^{α}-Benzyl-*N*′-(benzyloxycarbonyl)-N^{β},N^{β}-bis(*tert*-butyloxycarbonyl)glycinehydrazide (7h): M.p. 82 °C. IR (KBr): ṽ = 1772, 1731, 1715, 1682 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.45−7.20, (m, 10 H), 5.66−5.56 (m, 1 H), 5.19−5.08 (m, 2 H), 4.79−4.69 (m, 2 H), 4.01−3.88 (m, 2 H), 1.38 (s, 18 H) ppm. ^{13}C NMR: δ = 170.2, 164.7, 156.4, 136.7, 135.6, 135.2, 133.6, 130.2, 129.2, 128.9, 128.7, 128.5, 128.4, 124.6, 67.4, 52.0, 42.8 ppm. $C_{27}H_{35}N_7O_3$ (505.6): calcd. C 63.14, H 6.87, N 8.18; found C 63.13, H 6.78, N 8.20.

(*S*)-*N*′-(Benzyloxycarbonyl)-N^{β},N^{β}-bis(*tert*-butyloxycarbonyl)-N^{α}-methylalaninehydrazide (7i): IR (KBr): ṽ = 3327, 1802, 1770, 1728, 1685cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.33−7.22 (m, 5 H), 5.81 and 5.62 (2d, *J* = 8.5 Hz, 1 H), 5.09−5.00 (m, 2 H), 4.70−4.53 (m, 1 H), 3.26 and 3.08 (2 s, 3 H), 1.51 and 1.43 (2 s, 18 H), 1.35 and 1.23 (2 d, *J* = 6.5 Hz) ppm. ^{13}C NMR: δ = 175, 155.9, 155.5, 150.2, 149.7, 136.9, 128.8, 128.4, 128.2, 85.6.85.4, 84.2, 67.1, 47.3, 46.8, 38.2, 35.5, 28.2, 28.0, 19.4, 18.6 ppm. HRMS calcd. for $C_{22}H_{34}N_3O_7$ [M + H^+] 452.2397 *m*/*z*, found 452.2397.

(*S*)-*N*′-(Benzyloxycarbonyl)-N^{β},N^{β},*N*′-tris(*tert*-butyloxycarbonyl)-N^{α}-methylalaninehydrazide (7i′): ^1H NMR ($CDCl_3$): δ = 7.33−7.16 (m, 5 H), 5.19, 5.12 (2 s, 2 H), 4.91 (q, *J* = 6.8 Hz, 1 H), 3.05, 2.99 (2 s, 3 H), 1.40, 1.38 (2 s, 27 H), 1.32 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR: δ = 171.7, 153.2, 151.0, 150.2, 150.1, 135.5, 128.7, 128.6, 128.5, 84.9, 84.0, 68.9, 53.0, 35.9, 28.2, 16.2 ppm.

(*S*)-N^{α}-Benzyl-*N*′-(benzyloxycarbonyl)-N^{β},N^{β}-bis(*tert*-butyloxycarbonyl)alaninehydrazide (7j): IR (neat): ṽ = 1803, 1767, 1727, 1680 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.40−7.27 (m, 10 H), 5.69 (d,

J = 8.4 Hz, 1 H), 5.15−4.92 (m, 3 H), 4.78−4.48 (m, 2 H), 1.47 (s, 9 H), 1.32 (d, J = 6.1 Hz, 3 H), 1.20 (s, 9 H) ppm. ^{13}C NMR: δ = 175.2, 155.4, 150.3, 149.6, 136.9, 134.7, 130.9, 128.8, 128.7, 128.6, 128.4, 128.3, 85.2, 66.9, 52.0, 47.3, 28.1, 27.9, 22.4, 19.7 ppm. HRMS calcd. for $C_{28}H_{41}N_4O_7$ [M + NH_4^+] m/z = 545.2975 found 545.2975.

N^{α},N^{α},N^{β}-Tris(*tert*-butyloxycarbonyl)-N^{α}-cyclopentylhydrazine (7m): ^{1}H NMR ($CDCl_3$): δ 4.10 (quint, J = 8 Hz, 1 H), 1.72−1.62 (m, 4 H), 1.49−1.22 (m, 33 H) ppm. ^{13}C NMR: δ = 153.6, 151.1 ppm.

(*R*)-*N*-(*tert*-Butyloxycarbonyl)-N^{β},N^{β}-[bis(*tert*-butyloxycarbonyl)-amino]alanine Methyl Ester (7n): ^{1}H NMR ($CDCl_3$): δ = 4.48 (q, J = 7 Hz, 1 H), 3.68 (s, 3 H), 1.48, 1.47, 1.40 (3 s, 27 H), 1.28 (d, J = 7 Hz, 3 H) ppm. ^{13}C NMR: δ = 171.7, 153.8, 151.1, 83.9, 83.3, 82.1, 56.4, 52.2, 28.4, 28.2, 14.7 ppm. HRMS calcd. for $C_{19}H_{35}N_2O_8$ [M + H^+] m/z = 419.2393, found 419.2393.

N^{α}-(Benzyloxycarbonyl)-N^{β},N^{β}-bis(*tert*-butyloxycarbonyl)-N^{α}-methylhydrazine (7o): M.p. 92 °C. IR (KBr): $\tilde{\nu}$ = 1801, 1710 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.38−7.26 (m, 5 H), 5.19, 5.15 (2 s, 2 H), 3.15, 3.13 (2 s, 3 H), 1.47, 1.42 (2 s, 18 H) ppm. ^{13}C NMR: δ = 155.3, 150.2, 136.4, 128.8, 128.6, 128.3, 84.1, 68.4 and 68.1, 37.4 and 36.7, 28.2 ppm. $C_{19}H_{28}N_2O_6$ (380.4): calcd. C 59.98, H 7.42, N 7.36; found C 60.06, H 7.51, N 7.44.

N^{α}-Benzyl-N^{α}-(benzyloxycarbonyl)-N^{β},N^{β}-bis(*tert*-butyloxycarbonyl)hydrazine (7p): M.p. 65 °C. IR (KBr): $\tilde{\nu}$ = 1798, 1712 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.45−7.24 (m, 10 H), 5.20 (s, 2 H), 4.67 (s, 2 H), 1.36, 1.29 (2 s, 18 H) ppm. ^{13}C NMR: δ = 155.5, 150.3, 136.3, 135.4, 130.6, 130.2, 128.8, 128.7, 128.6, 128.4, 84.0, 68.7, 68.3, 54.9, 53.9, 28.1 ppm. $C_{25}H_{32}N_2O_6$ (456.5): calcd. C 67.77, H 7.06, N 6.13; found C 65.72, H 7.05, N 6.15.

N^{α}-(Benzyloxycarbonyl)-N^{β},N^{β}-bis(*tert*-butyloxycarbonyl)-N^{α}-cyclopentylhydrazine (7q): IR (neat): $\tilde{\nu}$ = 3065, 3033, 1801, 1753, 1722 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.38−7.21 (m, 5 H), 5.16−5.09 (m, 2 H), 4.37−4.18 (m, 1 H), 1.97−1.77 (m, 2 H), 1.72−1.29 (m, 24 H) ppm. ^{13}C NMR: δ = 154.9, 151.1, 136.5, 128.8, 128.4, 128.2, 83.9, 67.8, 61.4, 29.5, 28.3, 23.5 ppm. HRMS calcd. for $C_{23}H_{38}N_3O_6$ [M + NH_4^+] 452.2761 m/z, found 452.2774.

***(R)*-N^{α}-(Benzyloxycarbonyl)-N^{β},N^{β}-[bis(*tert*-butyloxycarbonyl)-amino]alanine Ethyl Ester (7r):** IR (neat): $\tilde{\nu}$ = 1800, 1764, 1734 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.38−7.26 (m, 5 H), 5.29−5.17 (m, 2 H), 4.58 (q, J = 7 Hz, 1 H), 4.20 (t, J = 7 Hz, 3 H), 1.51, 1.47, 1.45, 1.40 (4 s, 18 H), 1.36 (d, J = 7 Hz, 3 H), 1.26 (t, J = 7 Hz, 3 H) ppm. ^{13}C NMR: δ = 155.5, 150.3, 136.3, 135.4, 130.6, 130.2, 128.8, 128.7, 128.6, 128.4, 84.0, 68.7, 68.3, 54.9, 53.9, 28.1 ppm. HRMS calcd. for $C_{23}H_{38}N_3O_8$ [M + NH^+] 484.2659 m/z, found 484.2661.

Procedure for the Transprotection of Compound 6n with Pyrrolidine: Pyrrolidine (2 mM, 100 mg) was added to a solution of compound **6n** (1.5 mM, 540 mg) in THF (10 mL) at room temperature. The mixture was stirred at room temperature for 72 h. Boc_2O (3 mM, 650 mg) and a catalytic amount of DMAP were added. The mixture was stirred at room temperature for 3 h. The solvent was removed in vacuo and the residue was separated by column chromatography to give **11** (87 %). ^{1}H NMR ($CDCl_3$): δ = 7.63−7.02 (m, 14 H), 5.43 (d, J = 14 Hz, 1 H), 4.52 (d, J = 14 Hz, 1 H), 3.63−3.43 (m, 2 H), 3.31−3.20 (m, 2 H), 0.82 s, 9 H) ppm. ^{13}C NMR: δ = 173.3, 169.3, 168.2, 150.5, 131.0, 130.5, 129.7, 128.6, 128.5, 128.4, 128.1, 126.9, 126.1, 85.1, 52.6, 49.5, 46.2, 27.3, 26.5, 24.8 ppm. A solution of methylamine (1.5 mM, 2 M in MeOH) was added at room temperature to a solution of compound **11** (1 mM, 420 mg) in THF (10 mL). The mixture was stirred for 10 min at room temperature (until completion, monitored by TLC). The solvent and the excess methylamine were removed in vacuo. The solvent was removed in vacuo and the residue was separated by column chromatography to give compound **10f** in quantitative yield.

General Procedure for the Deprotection of Compounds 7 with $Mg(ClO_4)_2$: $Mg(ClO_4)_2$ (110 mg, 0.5 mM) was added to a stirring solution of compound **7** (3 mM) in CH_3CN (30 mL). The solution was stirred at room temperature for 3 h (monitored by TLC until completion) and then partitioned between water and diethyl ether. The aqueous layer was extracted twice with diethyl ether, and the combined organic layers were dried with $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed on silica gel with a mixture of hexane and EtOAc as eluent.

N^{α}-Acetyl-N^{β}-(*tert*-butyloxycarbonyl)-N^{α}-methylhydrazine (10a): M.p. 80 °C. IR (KBr): $\tilde{\nu}$ = 1731, 1637 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.71 (s, 1 H), 3.05 (s, 3 H), 2.01 (s, 3 H), 1.12 (s, 9 H) ppm. ^{13}C NMR: δ = 174.3, 154.7, 82.0, 36.0, 28.5, 20.7 ppm. $C_8H_{16}N_2O_3$ (188.2): calcd. C 51.05, H 8.57, N 14.88; found C 51.62, H 8.53, N 13.54.

N^{α}-Acetyl-N^{α}-Benzyl-N^{β}-(*tert*-butyloxycarbonyl)hydrazine (10b): M.p. 62−65 °C. IR (KBr): $\tilde{\nu}$ = 1730, 1655 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.34−7.12 (m, 5 H), 5.36−4.27 (m, 2 H), 2.02 (s, 3 H), 1.37 (s, 9 H) ppm. ^{13}C NMR: δ = 174.0, 154.6, 136.2, 129.3, 129.1, 128.1, 81.9, 50.8, 28.4, 20.1 ppm. HRMS calcd. for $C_{14}H_{21}N_2O_3$ [M + H^+] 265.1552 m/z, found 265.1551.

N^{β}-(*tert*-Butyloxycarbonyl)-N^{α}-methyl-N^{α}-heptanoylhydrazine (10c): M.p. < 50 °C. IR (KBr): $\tilde{\nu}$ = 1733, 1648 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.35−7.12 (m, 1 H), 3.08 (s, 3 H), 2.36−2.26 (m, 2 H), 1.61−1.50 (m, 2 H), 1.45 (s, 9 H), 1.31−1.18 (m, 8 H), 0.83 (t, J = 6 Hz, 3 H) ppm. ^{13}C NMR: δ = 176.6, 154.7, 81.9, 32.4, 32.1, 29.7, 29.4, 28.5, 25.1, 23.0, 14.4 ppm. $C_{13}H_{27}N_2O_3$ (259.4): calcd. C 60.20, H 10.49, N 10.80; found C 60.70, H 10.21, N 10.17.

N^{α}-Benzyl-N^{β}-(*tert*-butyloxycarbonyl)-N^{α}-heptanoylhydrazine (10d): M.p. 66 °C. IR (KBr): $\tilde{\nu}$ = 3261, 1729, 1642 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.37−7.19 (m, 5 H), 6.68−6.60 (m, 1 H), 5.61−4.95, 4.38−3.90 (2 m, 2 H), 2.46−2.29 (m, 2 H), 1.72−1.18 (m with s at 1.43, 18 H), 0.88 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR: δ = 176.2, 154.5, 136.4, 129.4, 129.1, 128.2, 82.1, 50.6, 32.7, 32.1, 29.7, 29.5, 28.5, 25.1, 23.0, 14.5 ppm. $C_{19}H_{31}N_2O_3$ (335.5): calcd. C 68.03, H 9.31, N 8.35; found C 68.48, H 9.38, N 8.14.

N^{α}-Benzoyl-N^{β}-(*tert*-butyloxycarbonyl)-N^{α}-methylhydrazine (10e): M.p. 112−114 °C. IR (KBr): $\tilde{\nu}$ = 3440, 1702, 1663 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.44−7.22 (m, 5 H), 3.23 (s, 3 H), 1.35 (s, 9 H) ppm. ^{13}C NMR: δ = 134.9, 130.6, 128.3, 127.6, 82.0, 28.4 ppm. $C_{13}H_{18}N_2O_3$ (250.3): calcd. C 62.38, H 7.25, N 11.19; found C 62.53, H 7.26, N 11.21.

N^{α}-Benzoyl-N^{α}-benzyl-N^{β}-(*tert*-butyloxycarbonyl)hydrazine (10f): M.p. 124 °C. IR (KBr): $\tilde{\nu}$ = 3223, 1726, 1645 cm^{-1}. ^{1}H NMR ($CDCl_3$): = δ 7.62−7.22 (m, 10 H), 6.75 (s, 1 H), 6.61−4.07 (m, 2 H), 1.31 (s, 9 H) ppm. ^{13}C NMR: δ = 154.4, 136.2, 135.3, 130.5, 129.1, 129.0, 128.3, 128.0, 127.7, 82.0, 28.6 ppm. $C_{19}H_{22}N_2O_3$ (326.4): calcd. C 69.92, H 6.79, N 8.58; found C 69.72, H 6.79, N 8.72.

N'-(Benzyloxycarbonyl)-N^{β}-(*tert*-butyloxycarbonyl)-N^{α}-methylglycinehydrazide (10g): IR (neat): $\tilde{\nu}$ = 1720, 1670 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 9.57−9.48 (m, 1 H), 7.42−7.28 (m, 5 H), 5.04 (s, 2 H), 4.09−3.47 (m, 2 H), 2.97 (s, 3 H), 1.44 (s, 9 H) ppm. ^{13}C NMR:

δ = 171.7, 157.3, 155.2, 137.9, 129.2, 128.6, 128.5, 81.4, 66.2, 42.2, 36.0, 28.8 ppm. $C_{16}H_{23}N_3O_5$ (337.4): calcd. C 56.96, H 6.87, N 12.45; found C 56.75, H 6.90, N 12.48.

N^{α}-Benzyl-N'-(benzyloxycarbonyl)-N^{β}-(*tert*-butyloxycarbonyl)-glycinehydrazide (10h): M.p. 146 °C. IR (KBr): ṽ = 3460, 1724, 1634 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.42−7.21 (m, 10 H), 7.08−7.00 (m, 1 H), 5.79−5.67 (m, 1 H), 5.54−4.95 (m, 2 H), 4.47−3.80 (m, 3 H), 1.43 (s, 9 H) ppm. ^{13}C NMR: δ = 171.5, 156.8, 154.3, 136.8, 135.2, 129.5, 129.2, 128.9, 128.5, 128.4, 82.9, 67.3, 51.2, 42.9, 28.5 ppm.

(*S*)-N'-(Benzyloxycarbonyl)-N^{β}-(*tert*-butyloxycarbonyl)-N^{α}-methyl-alaninehydrazide (10i): IR (KBr): ṽ = 1723, 1667 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.94−7.80 (m, 1 H), 7.38−7.22 (m, 5 H), 5.98−5.86 (m, 1 H), 5.13−4.72 (m, 2 H), 3.09 (s, 3 H), 1.45 (s, 9 H), 1.28 (d, *J* = 7 Hz, 3 H) ppm. ^{13}C NMR: δ = 175.8, 156.3, 154.7, 136.8, 128.8, 128.4, 128.3, 82.4, 67.1, 47.0, 36.0, 28.3, 18.5 ppm. HRMS calcd. for $C_{17}H_{29}N_4O_5$ [M + NH_4^+] 369.2138 *m*/*z*, found 369.2134.

(*S*)-N^{α}-Benzyl-N'-(benzyloxycarbonyl)-N^{β}-(*tert*-butyloxycarbonyl)-alaninehydrazide (10j): IR (neat): ṽ = 3288, 1718, 1666 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.42−7.09 (m, 10 H), 6.14−5.96 (m, 1 H), 5.19−4.69 (m, 4 H), 4.33−4.07 (m, 1 H), 1.43 (s, 9 H), 1.34 (d, *J* = 6 Hz, 3 H) ppm. ^{13}C NMR: δ = 175.7, 156.4, 154.5, 136.7, 135.5, 129.4, 129.3, 129.1, 128.8, 128.4, 82.2, 67.1, 50.7, 47.3, 28.5, 24.2, 18.5 ppm. HRMS calcd. for $C_{23}H_{30}N_3O_5$ [M + H^+] *m*/*z* = 428.2185 found 428.2188.

N^{α},N^{β}-Bis(*tert*-butyloxycarbonyl)-N^{α}-(cyclopentyl)hydrazine (10m): ^1H NMR ($CDCl_3$): δ = 6.25−5.99 (m, 5 H), 4.57−4.36 (m, 1 H), 1.86−1.37 (m with s at 1.46, 17 H) ppm. ^{13}C NMR: δ = 156.3, 155.4, 81.2, 59.5, 29.3, 28.5, 24.0 ppm. HRMS calcd. for $C_{15}H_{28}N_2O_4$ 300.2049 *m*/*z*, found 300.2045.

(*R*)-N^{α}(*tert*-Butyloxycarbonyl)-N^{β}-[(*tert*-butyloxycarbonyl)amino]-alanine Methyl Ester (10n): ^1H NMR ($CDCl_3$): δ = 6.49−6.28 (m, 1 H), 4.98−4.85 (m, 1 H), 3.68 (s, 3 H), 1.60−1.26 (m, 21 H) ppm. ^{13}C NMR: δ = 173.3, 155.4, 82.1, 52.6, 28.5, 14.7 ppm. $C_{14}H_{26}N_2O_6$: calcd. C 52.81, H 8.23, N 8.80; found C 52.94, H 8.15, N 8.82.

N^{α}-(Benzyloxycarbonyl)-N^{β}-(*tert*-butyloxycarbonyl)-N^{α}-(methyl)-hydrazine (10o): M.p. 63 °C. IR (KBr): ṽ = 3278, 1694. ^1H NMR ($CDCl_3$): δ = 7.39−7.24 (m, 5 H), 5.14 (s, 2 H), 3.17 (s, 3 H), 1.42 (s, 9 H) ppm. ^{13}C NMR: δ = 156.8, 136.5, 128.8, 128.5, 128.3, 81.8, 68.2, 38.3, 28.6 ppm. $C_{14}H_{20}N_2O_4$: calcd. C 59.98, H 7.19, N 9.99; found C 59.90, H 7.24, N 10.04.

N^{α}-Benzyl-N^{α}-(benzyloxycarbonyl)-N^{β}-(*tert*-butyloxycarbonyl)-hydrazine (10p): M.p. 66 °C. IR (KBr): ṽ = 3265, 1709 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.57−7.06 (m, 10 H), 6.68−6.17 (m, 1 H), 5.23 (s, 2 H), 4.75 (s, 2 H), 1.44 (s, 9 H) ppm. ^{13}C NMR: δ = 156.7, 136.9, 136.4, 129.2, 129.0, 128.6, 128.3, 128.2, 128.1, 82.0, 68.6, 54.0, 28.5 ppm. $C_{20}H_{24}N_2O_4$: calcd. C 67.40, H 6.79, N 7.86; found C 67.49, H 6.79, N 7.89.

N^{α}-(Benzyloxycarbonyl)-N^{β}-(*tert*-butyloxycarbonyl)-N^{α}-cyclopentyl-hydrazine (10q): ^1H NMR ($CDCl_3$): δ = 7.40−7.24 (m, 5 H), 6.54−6.40 (m, 1 H), 5.30−4.97 (m, 2 H), 4.66−4.46 (m, 1 H), 1.94−1.23 (m, 18 H) ppm. ^{13}C NMR: δ = 156.2, 136.5, 128.8, 128.4, 128.3, 81.5, 68.2, 29.3, 24.1 ppm.

(*R*)-*N*-Benzyloxycarbonyl-*N*-[(*tert*-butyloxycarbonyl)amino]alanine Ethyl Ester (10r): IR (neat): ṽ = 1737, 1718 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.39−7.26 (m, 5 H), 6.69−6.52 (m, 1 H), 5.22 ("d", 1 H), 5.10 ("d", 1 H), 5.05−4.95, 4.85−4.73 (2 m, 1 H), 4.23−4.03 (m, 2 H), 1.47 (d, *J* = 7 Hz, 3 H), 1.39, 1.35 (2 s, 9 H), 1.29−1.14 (m, 3 H) ppm. ^{13}C NMR: δ = 172.6, 156.4, 155.5, 136.1, 128.8, 128.5, 128.1, 81.6, 68.7, 61.8, 28.4, 14.5 ppm. HRMS calcd. for $C_{18}H_{30}N_3O_6$ [M + NH_4^+] 384.2135 *m*/*z*, found 384.2126.

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Received July 17, 2003

