Urethane *N*-Carboxyanhydrides from *β*-Amino Acids

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A general method has been developed for the synthesis of *N*-*tert*-butyloxycarbonyl *N*-carboxyanhydrides from *β*-amino acids using Vilsmeier complex. These *β*-UNCA are stable, and the reactivity with different nucleophiles (alcohol, amine, lithium enolate) was studied.

Introduction

The use of *N*-carboxyanhydride (NCA) derivatives in peptide synthesis is a particularly attractive strategy and has been quite extensively used.[1] There is literature precedence for formation of five-membered *N*-carboxyanhydrides, with the most conventional procedure involving reaction of an amino acid with a large excess of phosgene.[2] This method is unattractive primarily because of the toxicity of phosgene and because of the harsh temperatures required to drive the reaction. However, the interest in NCA's has resulted in alternative procedures being explored. Some examples include trichloromethyl carbamate[3] and bis trichloromethyl carbonate,[4] both of which are phosgene precursors, and phosphorus trichloride,[2,5] which enables the reaction to occur at lower temperatures. However, results reported are very substrate dependent.

The tendency of NCA derivatives to polymerize has stimulated the synthesis of UNCA's in which the nitrogen is protected by a carbamate group.[6] Urethane *N*-carboxyanhydrides (UNCA's) are attractive target molecules for medicinal chemists as they have incorporated into their structure an activated carboxylate group and a protected amino group. Such molecules are highly reactive and lend themselves to facile stepwise peptide synthesis and solid-phase synthesis. One of the most successful strategies employed to incorporate α-amino acids into biologically active compounds is via the corresponding urethane *N*-carboxyanhydrides, which are very reactive compounds and react with nucleophiles to yield readily removable side products. Moreover, urethane *N*-carboxyanhydrides can be considered as starting material for the synthesis of various amino acid derivatives.[7] Recently considerable attention has been directed toward understanding the biological activity of *β*-amino acids and their derivatives. *β*-Amino acids are found as components of peptidic[8] and natural products[9] with antibiotic, antifungal, and cytotoxic properties. Recently, significant progress has been made in elucidating the conformational properties[10] of short polymers of *β*-amino acids; *β*-peptides are promising antimicrobial candidates[11] because they offer a choice of secondary structures and because the unnatural *β*-peptide backbone is resistant to protease degradation.[12]

The intent of this study was to synthesize *N*-*tert*-butyloxycarbonyl-protected *N*-carboxyanhydride derivatives of *β*-amino acids. Should their synthesis be successful, we hoped to carry out further studies to understand the stability and utility of these compounds. Alternatively, we decided to investigate the synthesis of *N*-carboxyanhydride derivatives of *β*-amino acids, starting first with *β*-alanine.

Results

β-Alanine *N*-carboxyanhydride **4** was selected as the primary target as it was considered to be the most synthetically challenging, due to its flexibility.

The synthesis of *N*-carboxyanhydrides from *β*-amino acids using phosgene was first reported 45 years ago by L. Birkofer,[13−15] followed by H. R. Kricheldorf,[16] who also studied their polymerization with basic catalysts, and recently (during this work) by T. J. Deming.[17]

The first procedure we applied to the formation of *β*-alanine *N*-carboxyanhydride was "Leuch's method",[6] which utilizes phosphorus trichloride. Several reactions failed to afford the desired six-membered NCA **4** (Scheme 1). An alternative Lewis acid was employed, PBr_3.

The first attempt successfully afforded *β*-Ala-NCA **4**; unfortunately the unstablility of this molecule was real-

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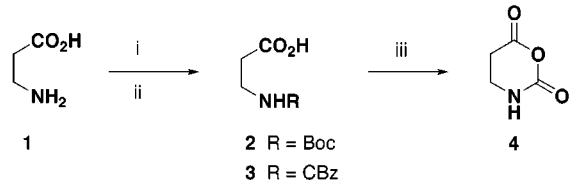
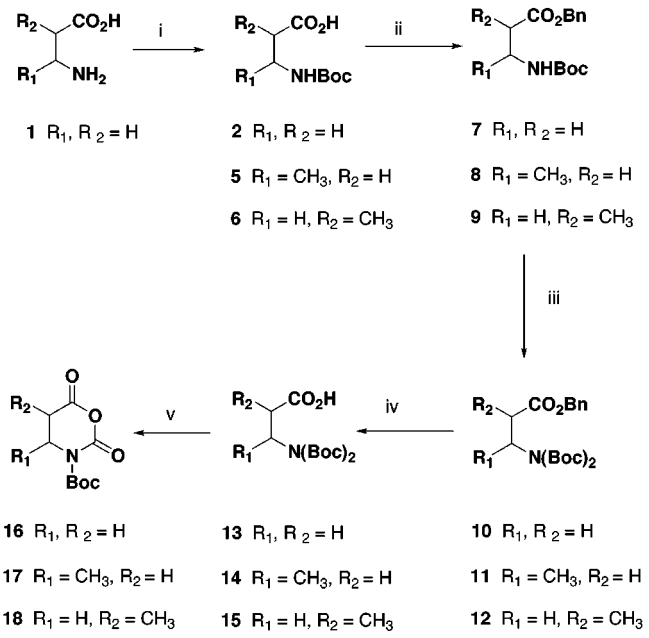
Scheme 1[a]



[a] Reagents and conditions: i, $(Boc)_2O$, NaOH, H_2O, ^{t}BuOH, 30 °C, 18 H, 73%; ii, NaOH, H_2O, $C_6H_5O_2CCl$, rt, 18 h; iii, PBr_3, CH_2Cl_2, 0 °C, 4 h.

Scheme 2[a]



[a] Reagents and conditions: i, $(Boc)_2O$, NaOH, H_2O, ^{t}BuOH, 30 °C, 18 H, 73%; ii, Cs_2CO_3, MeOH/H_2O, then BnBr, DMF, 18H, rt, 18 h; iii, $(Boc)_2O$, DMAP (10%), CH_3CN, 12−24 h; iv, Pd/C, H_2, 1 H, rt; v, ClCOCOCl, DMF, CH_3CN, at −20 °C, then addition of **13** or **14** or **15**, pyr., CH_3CN, −20 °C for 2 h, then 0 °C for 1 h followed by 4 h at rt.

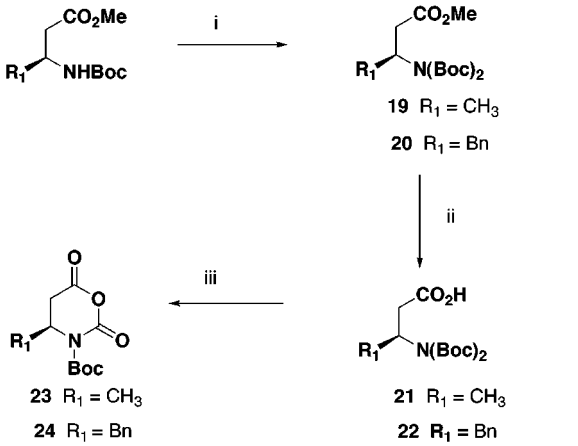
ized (air and temperature sensitive). To synthesize *N*-*tert*-butyloxycarbonyl-protected *N*-carboxyanhydride derived from *β*-alanine we carried out the procedure outlined by Wakselman[18] (Scheme 2), affording the desired UNCA in varying yields. A slight modification to the formation of the dimethylformamide−imide salt resulted in much improved yields, 8−40% to 55−60%, using the more conventional DMF/oxalyl chloride in acetonitrile. After addition of the pyridinium salt of the chosen bis Boc amino acid to the imide salt, the corresponding Boc *N*-carboxyanhydride was afforded in good yield after recrystallization from EtOAc/hexane at low temperature (55−60%).

This synthetic scheme was applied to the synthesis of *N*-Boc-*β*-Ala *N*-carboxyanhydride **16**, *N*-Boc-*β*-methyl-*β*-alanine *N*-carboxyanhydride **17** and racemic *N*-Boc-α-methyl-*β*-alanine *N*-carboxyanhydride **18** from respectively *β*-alanine, DL-3-aminobutyric acid, and DL-3-aminoisobutyric acid according to Scheme 2. We tried to optimize the yields and particularly step v (Scheme 2) by varying the conditions; the results for **17** are reported

Table 1. Optimization of the Reaction Conditions

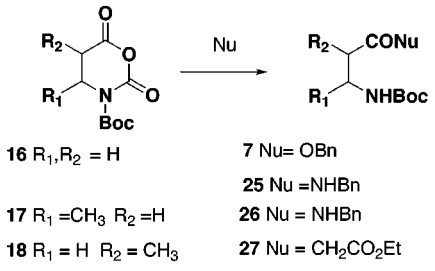
no.	time at −20 °C	time at 0 °C	time at rt	equiv of imide salt	yield (%)
1	2 h	30 min	4 h	2	63
2	2 h	30 min	4 h	4	54
3	2 h	30 min	4 h	6	62
4	2 h	30 min	4 h	2	55
5	30 min	30 min	3 h	1.1	0
6		30 min	2 h	6	69 crude

Scheme 3[a]



[a] Reagents and conditions: i, $(Boc)_2O$, DMAP (10%), CH_3CN, 12−48 h; ii, NaOH, dioxane/H_2O; iii, ClCOCOCl, DMF, CH_3CN, at −20 °C, then addition of **21** or **22**, pyr., CH_3CN, −20 °C for 2 h, then 0 °C for 1 h followed by 4 h at rt.

Scheme 4



in Table 1. For the *β*-sustituted *β*-alanine derivatives, greater reaction times at low temperature failed to improve the yields. Presently the optimal conditions require 2 equiv of the imide salt and just 15 min at −20 °C, followed by 2 h at rt. The synthetic route employed to obtain the asymmetric *N*-Boc *β*-alanine *N*-carboxyanhydride is shown in Scheme 3.

Having sucessfully formed several *β*-alanine *N*-*tert*-butyloxycarbonyl *N*-carboxyanhydrides, we were interested in understanding the utility of these compounds. Nucleophilic attack of benzylamine, benzyl alcohol, and the lithium enolate of ethyl acetate on the UNCA derivatives of *β*-amino acids including **16**, **17**, and **18** proved to be very rapid, and a clean reaction was obtained (Scheme 4). We[19] have described that reduction of UNCA derivatives of α-amino acids with $LiAlH_4$ produced the corresponding aldehydes in fairly good conditions. Reduction of the UNCA derivatives of *β*-amino acids (e.g., Boc-*β*-Ala NCA) under the same conditions yielded only the corresponding alcohol instead of the desired aldehydes.

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Conclusion

A general strategy for the synthesis of *N*-*tert*-butyloxycarbonyl *β*-amino acid *N*-carboxyanhydrides has been accomplished; these derivatives are crystalline and stable. However they showed a high reactivity toward nucleophiles. We have begun to understand the stability and reactivity of these compounds; however, there is still much work to be done to fully understand the utility of *N*-protected *β*-alanine *N*-carboxyanhydrides.

Experimental Section

All reactions were conducted under a positive pressure of argon at ambient temperature unless otherwise indicated. Temperatures designated 0, −20, or −30 °C are approximate and refer to bath temperature. Silica gel (70−230) mesh was used for column chromatography. Acetonitrile was distilled from CaH_2 immediately before use. ^{1}H NMR spectra were recorded on a Bruker at 200 MHz in $CDCl_3$ unless otherwise indicated. Mass spectra were recorded on JEOL DX 300 and SX 102. Infrared spectra were performed on a Perkin-Elmer Paragon 1000. Melting points are uncorrected.

3-(*tert*-Butyloxycarbonylamino)propionic Acid (*N*-Boc-*β*-alanine, 2). To a solution of *β*-alanine (2.0 g, 22 mmol) in H_2O (12 mL) were added di-*tert*-butyl dicarbonate (4.85 g, 22 mmol), sodium hydroxide (1.0 g, 25 mmol) in H_2O (10 mL), and 2-methyl-2-propanol (16.5 mL). The reaction mixture was heated to 30 °C and stirred at room temperature. After 18 h, the solution was evaporated in vacuo and H_2O added (50 mL). The product was extracted into EtOAc (3 × 30 mL), dried ($MgSO_4$), and evaporated to dryness under vacuum to afford 3.10 g (73%) of the desired product: R_f 0.85 (EtOH/NH_4OH, 3:2); ν_{max} cm^{-1} (film) 3438 (N−H), 2967 (C−H), 1704 (C═O), 1510, 1238; ^{1}H NMR ($CDCl_3$) δ 10.10 (1H, br s, CO_2H), 5.12 (1H, br s, NH), 3.06−3.77 (2H, m), 2.39−2.84 (2H, m), 1.46 (9H, s, ^{t}Bu).

Using the same procedure, **5** and **6** were prepared.

3-(*tert*-Butyloxycarbonylamino)butyric Acid (*N*-Boc-*β*-methyl-*β*-alanine, 5): 99%; R_f 0.24 (MeOH/CH_2Cl_2, 95:5); ^{1}H NMR ($CDCl_3$) δ 5.00 (1H, br s, NH), 4.06−4.09 (1H, m, C*H*CH_3), 2.51−2.59 (2H, m), 1.47 (9H, s, ^{t}Bu), 1.29 (3H, t, J = 6.8).

2-Methyl-3-(*tert*-butyloxycarbonylamino)propionic acid (*N*-Boc-α-methyl-*β*-alanine, 6): 99%; R_f 0.74 (EtOH/NH_4-OH, 4:1); ^{1}H NMR ($CDCl_3$) δ 7.30 (1H, br s, CO_2H), 5.06 (1H, br s, NH), 3.47−3.25 (2H, m), 2.82−2.63 (2H, m), 1.46 (9H, s, ^{t}Bu), 1.29 (3H, d, J = 7.7, CH_3).

Benzyl 3-(*tert*-Butyloxycarbonylamino)propionate (*N*-Boc-*β*-alanine benzyl ester, 7). *N*-Boc-*β*-alanine (400 mg, 2.1 mmol) was dissolved in MeOH/H_2O (10/1, 22 mL) and treated with cesium carbonate (342 mg, 1.05 mmol) until the solution was neutralized. The resulting cesium salt was evaporated to dryness and redissolved in DMF (8 mL). Benzyl bromide (251 μL, 2.1 mmol) was added dropwise to the cesium salt. After 22 h, the DMF was evaporated and the residue treated with H_2O (30 mL) and EtOAc (3 × 25 mL). The combined organic phases were dried ($MgSO_4$) and evaporated under vacuum to give 534 mg (90%) of *N*-Boc-*β*-alanine benzyl ester: R_f 0.38 (hex/EtOAc, 4:1); *m*/*z* (ES) 581 ($2M^+$ + Na), 279 (M^+ + 1), 179 (−Boc); ^{1}H NMR ($CDCl_3$) δ 7.28−7.40 (5H, m, ArH), 5.18 (2H, s, C$H_2C_6H_5$), 5,10 (1H, br s, NH), 3.45 (2H, t, J = 6.0), 2.61 (2H, t, J = 6.0), 1.45 (9H, s, ^{t}Bu).

Using the same procedure, **8** and **9** were synthesized.

Benzyl 3-(*tert*-butyloxycarbonylamino)butyrate (*N*-Boc-*β*-methyl-*β*-alanine benzyl ester, 8): 91%; R_f 0.39 (hex/EtOAc, 6:1); *m*/*z* (ES) 294 (M^+ + 1), 179 (−^{t}Bu); ^{1}H NMR ($CDCl_3$) δ 7.40−7.37 (5H, m, ArH), 5.15 (2H, s, C$H_2C_6H_5$), 4.92 (1H, br s, NH), 4.11−4.01 (1H, m, C*H*CH_3), 2.60 (2H, ddd, J 21.0, 15.5, 5.5, CH_2), 1.45 (9H, s, ^{t}Bu), 1.24 (3H, d, J 6.8, CHCH_3).

Benzyl 2-methyl-3-(*tert*-butyloxycarbonylamino)propionate (*N*-Boc-α-methyl-*β*-alanine benzyl ester, 9): 84%; R_f 0.36 (hex/EtOAc, 6:1); *m*/*z* (ES) 294 (M^+ + 1); ^{1}H NMR ($CDCl_3$) δ 7.40−7.32 (5H, m, ArH), 5.18 (2H, s, C$H_2C_6H_5$), 4.91 (1H, br s, NH), 3.21−3.45 (2H, m), 2.72−2.69 (1H, m), 1.45 (9H, s, ^{t}Bu), 1.24 (3H, d, J = 6.8, CHCH_3).

Benzyl 3-(Di-*tert*-butyloxycarbonylaminopropionate) (*N*-Bis-Boc-*β*-alanine benzyl ester, 10). *N*-Boc-*β*-alanine benzyl ester (384 mg, 1.4 mmol) was dissolved in freshly distilled acetonitrile (8 mL). Di-*tert*-butyl dicarbonate (326 mg, 1.5 mmol) was added to the solution, followed by DMAP (16 mg, 5% w/w). After 12 h of stirring at room temperature, starting material remained, so a further 2 equiv of Boc-anhydride and DMAP were added at 12 h intervals. The reaction was treated with H_2O (10 mL) and the product extracted into EtOAc (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and evaporated under vacuum to give 320 mg (61%) of *N*-bis Boc-*β*-alanine benzyl ester: R_f 0.46 (hex/EtOAc, 4:1); *m*/*z* (ES) 380 (M^+ + 1); ^{1}H NMR ($CDCl_3$) δ 7.40−7.30 (5H, m, ArH), 5.12 (2H, s, C$H_2C_6H_5$), 3.94 (2H, t, J = 7,6), 2.69 (2H, t, J = 7,0), 1.51 (18H, s, 2 × ^{t}Bu).

Using the same procedure, **11** and **12** were obtained.

Benzyl 3-(di-*tert*-butyloxycarbonylamino)butyrate (*N*-bis-Boc-*β*-methyl-*β*-alanine benzyl ester, 11): 60%; R_f 0.60 (hex/EtOAc, 6:1); *m*/*z* (ES) 390 (M^+ + 1); ^{1}H NMR ($CDCl_3$) δ 7.38−7.29 (5H, m, ArH), 5.33 (1H, AB d, J = 12.3), 5.14 (1H, AB d, J = 12.3), 4.85−4.67 (1H, m, C*H*CH_3), 3.04 (1H, dd, J = 15.7, 7.5), 2.77 (1H, dd, J = 15.6, 7.2), 1.51 (9H, s, ^{t}Bu), 1.38 (3H, d, J = 6.9, CHCH_3).

Benzyl 2-methyl-3-(di-*tert*-butyloxycarbonylamino)-propionate (*N*-bis-Boc-α-methyl-*β*-alanine benzyl ester, 12): 81%; R_f 0.57 (hex/EtOAc, 4:1); *m*/*z* (ES) 390 (M + H^+); ^{1}H NMR ($CDCl_3$) δ 7.37−7.29 (5H, m, ArH), 5.17 (1H, AB d, J = 12.5, C$H_2C_6H_5$), 5.09 (1H, AB d, J = 12.5, C$H_2C_6H_5$), 3.83 (1H, dd, J = 14.0, 6.5), 3.68 (1H, dd, J = 14.0, 7.3), 2.96−2.86 (1H, m, C*H*CH_3), 1.49 (18H, s, 2 × ^{t}Bu), 1.19 (3H, d, J = 7.0).

3-(Di-*tert*-butyloxycarbonylamino)propionic Acid (*N*-Bis-Boc-*β*-alanine, 13). A solution of *N*-bis-Boc-*β*-alanine benzyl ester (320 mg, 0.8 mmol) in methanol (9 mL) was added to a suspension of palladium hydroxide on carbon (32 mg, 10% w/w) in methanol (10 mL), and the solution was hydrogenated. After 2 h, the suspension was filtered through Celite and the filtrate evaporated to dryness to afford the desired compound as a white powder (239 mg, 98%): R_f 0.48 (MeOH/CH_2Cl_2, 95:5); mp 102−103 °C; *m*/*z* (ES) 312 (M^+ + Na); ^{1}H NMR ($CDCl_3$) δ 3.90 (2H, t, J = 7.0), 2.72 (2H, t, J = 7.5), 1.52 (18H, s, 2 × ^{t}Bu).

Using the same procedure, **14** and **15** were prepared.

3-(Di-*tert*-butyloxycarbonylamino)butyric acid (*N*-bis-Boc-*β*-methyl-*β*-alanine, 14): 82%; mp 79−80 °C; R_f 0.52 (MeOH/CH_2Cl_2, 95:5); *m*/*z* (ES) 304 (M^+ + 1); ^{1}H NMR ($CDCl_3$) δ 4.63−4.80 (1H, m), 3.06 (1H, dd, J = 16.3, 7.5), 2.74 (1H, dd, J = 16.3, 7.0), 1.51 (18H, s, 2 × ^{t}Bu), 1.38 (3H, d, J = 6.9, CHCH_3).

2-Methyl-3-(di-*tert*-butyloxycarbonylamino)propionic acid (*N*-bis-Boc-α-methyl-*β*-alanine, 15): white powder (86%); R_f 0.64 (MeOH/CH_2Cl_2, 4:1); mp 49−50 °C; *m*/*z* (ES) 304 (M^+ + 1), 248 (M^+ − ^{t}Bu), 204 (M^+ − Boc); ^{1}H NMR ($CDCl_3$) δ 3.97 (1H, dd, J = 14.1, 7.3), 3.72 (1H, dd, J = 14.1, 7.0), 2.96−2.78 (1H, m, C*H*CH_3), 1.50 (18H, s, 2 × ^{t}Bu), 1.18 (3H, d, J = 7.1, CHCH_3).

3-*tert*-Butyloxycarbonyl-4,5-dihydro-1,3-oxazine-2,6-dione (*N*-Boc-*β*-alanine *N*-carboxyanhydride, 16). To a cooled (−20 °C) solution of DMF (804 μL, 10.4 mmol) in freshly distilled acetonitrile (5 mL) was added dropwise oxalyl chloride (907 μL, 10.4 mmol). After 30 min of stirring at −20 °C, a cooled solution (−20 °C) of *N*-bis-Boc-*β*-alanine (500 mg, 1.7 mmol) and pyridine (140 μL, 1.73 mmol) in acetonitrile (3 mL) was added dropwise. The solution was stirred at −20 °C for 2 h and then allowed to warm to room temperature (over 1 h) and stirred for a further 4 h. The reaction was quenched by pouring onto ice and the product extracted into EtOAc (3 × 10 mL), dried ($MgSO_4$), and evaporated under vacuum to afford the desired Boc-*β*-Ala NCA as a crude oil; recrystallization from ethyl acetate gave 231 mg (62%): mp 102−103 °C; *m*/*z* (FAB positive) 216 (M + H^+) (found: C, 50.31, H, 6.07, N, 6.49; $C_9H_{13}NO_5$ requires C, 50.23, H, 6.09, N, 6.51); ν_{max} cm^{-1} (film)

2982, 2935, 1825, 1787, 1745; ^{1}H NMR ($CDCl_3$) δ 3.94 (2H, t, J = 6.2), 2.90 (2H, t, J = 6.4), 1.57 (18H, s, 2 × ^{t}Bu).

Using the same procedure, **17** and **18** were prepared.

3-*tert*-Butyloxycarbonyl-4-methyl-4,5-dihydro-1,3-oxazine 2,6-dione (*β*-methyl-*β*-alanine *N*-carboxyanhydride, 17): white needles, (62%); mp 144−145 °C; *m*/*z* (FAB) 230 (M^+ +1) (found: C, 52.19, H, 6.72, N, 6.13; $C_{10}H_{15}NO_5$ requires C, 52.40, H, 6 0.60, N, 6.11); ν_{max} cm^{-1} (film) 2980, 2928, 1814, 1792, 1774; ^{1}H NMR ($CDCl_3$) δ 4.71−4.57 (1H, m, C*H*CH_3), 3.05 (1H, dd, J = 16.6, 5.9), 2.82 (1H, dd, J = 16.6, 2.0), 1.59 (9H, s, ^{t}Bu), 1.40 (3H, d, J = 6.7, CHC*H*$_3$).

3-*tert*-Butyloxycarbonyl-5-methyl-4,5-dihydro-1,3-oxazine-2,6-dione (*N*-Boc-α-methyl-*β*-alanine *N*-carboxyanhydride, 18): 62%; mp 89−90 °C; *m*/*z* (FAB) 230 (M^+ + 1) (found: C, 52.21, H, 6.72, N, 6.21; $C_{10}H_{15}NO_5$ requires C, 52.40, H, 6.60, N, 6.11); ^{1}H NMR ($CDCl_3$) δ 4.20 (1H, dd, J 13.2, 5.8), 3.49 (1H, dd, J = 13.1, 11.8), 3.00−2.73 (1H, m), 1.52 (9H, s, ^{t}Bu), 1.39 (3H, d, J = 6.9).

(*S*)-Methyl 3-(di-*tert*-butyloxycarbonylamino)butyrate (bis-Boc-*β*-methyl-*β*-alanine methyl ester, 19) was prepared by following the procedure described for **10**. Purification by column chromatography (4:1, hexane/EtOAc) afforded the desired product (50% conversion) and starting material: R_f 0.51 (hex/EtOAc, 6:1); *m*/*z* (ES) 286 (M + H^+); ^{1}H NMR ($CDCl_3$) δ 4.80−4.63 (1H, m, C*H*CH_3), 3.68 (3H, s, CO_2CH_3), 2.96 (1H, dd, J = 15.6, 7.5, CH_2), 2.71 (1H, dd, J = 15.6, 7.2, CH_2), 1.53 (18H, s, 2 × ^{t}Bu), 1.32 (3H, d, J = 6.9); $[\alpha]^{20}_D$ = +27 (c = 1, CH_2Cl_2).

(*S*)-3-(Di-*tert*-butyloxycarbonylamino)butyric Acid (Bis-Boc-*β*-methyl-*β*-alanine, 21). Bis-Boc-*β*-methyl-*β*-alanine methyl ester (179 mg, 0.6 mmol) was added to a solution of sodium hydroxide (28 mg, 0.7 mmol) in dioxane/H_2O (1 mL, 1:9), and the solution was stirred at rt overnight. The dioxane was removed under vacuum, and then the residue was treated with 10% citric acid followed by EtOAc (3 × 5 mL). The organic phases were combined, dried ($MgSO_4$), and evaporated under vacuum to afford 137 mg (95%) of the product as a white powder: mp 79−80 °C; ^{1}H NMR ($CDCl_3$) δ 4.80−4.63 (1H, m, C*H*CH_3), 3.07 (1H, dd, J = 16.4,7.5, CH_2), 2.75 (1H, dd, J = 16.4, 7.0, CH_2), 1.52 (18H, s, 2 × ^{t}Bu), 1.39 (3H, d, J = 6.9); $[\alpha]^{20}_D$ = +32 (c = 1, CH_2Cl_2).

(*S*)-3-*tert*-Butyloxycarbonyl-4-methyl-4,5-dihydro-1,3-oxazine-2,6-dione (Boc-*β*-methyl-*β*-alanine *N*-carboxyanhydride, 23). Following the procedure described for **16**, Boc-*β*-methyl-*β*-Ala NCA was obtained as a crude oil. Recrystallization from ethyl acetate gave white needles (53%): *m*/*z* (ES positive) 481 ($2M^+$ + Na), 252 (M^+ + Na), 230 (M^+ + 1), 174 (M^+ − 56). Spectroscopic data obtained were the same as given for compound **17**. $[\alpha]^{20}_D$ = −68 (c = 1, CH_2Cl_2).

(*S*)-Methyl 3-(Di-*tert*-butyloxycarbonylamino)-4-phenylbutyrate (Bis-Boc-*β*-homo-phenylalanine methyl ester, 20). Following the procedure described for **10** and purification carried out using column chromatography in hexane/EtOAc (5:1) afforded the desired product (45%) and starting material: R_f 0.52 (hex/EtOAc, 6:1); *m*/*z* (ES) 394 (M^+ + 1), 338 (M^+ − 56), 382 (M^+ − 112); ^{1}H NMR ($CDCl_3$) δ 7.16−7.34 (5H, m, ArH), 4.91−4.81 (1H, m, C*H*CH_3), 3.23 (1H, dd, J = 13.4, 8.7), 3.07−2.88 (2H, m), 2.73 (1H, dd, J = 15.8, 6.2), 1.45 (18H, s, 2 × ^{t}Bu); $[\alpha]^{20}_D$ = −38 (c = 1, CH_2Cl_2).

(*S*)-3-(Di-*tert*-butyloxycarbonyamino)-4-phenylbutyric acid (bis-Boc-*β*-homo-phenylalanine, 22) was prepared by following the procedure described for **21**: 68%; R_f 0.6 (MeOH/CH_2Cl_2, 6:1); ^{1}H NMR ($CDCl_3$) δ 9.91 (1H, br s, CO_2H), 7.19−7.31 (5H, m), 4.94−4.84 (1H, m), 3.20−2.90 (3H, m), 2.75 (1H, dd, J = 16.6,6.1), 1.44 (18H, s, 2 × ^{t}Bu.); $[\alpha]^{20}_D$ = −30 (c = 1, CH_2Cl_2).

(*S*)-3-*tert*-Butyloxycarbonyl-4-benzyl-4,5-dihydro-1,3-oxazine-2,6-dione (Boc-*β*-homo-phenylalanine *N*-carboxyanhydride, 24). Following the procedure described for **16**, Boc-*β*-homo-phe-Ala NCA was obtained as a crude oil and recrystallized from ethyl acetate (65%): mp 114−115 °C; *m*/*z* (ES positive) 306 (M^+ + 1), 291 (M^+ − 15), 279 (M^+ − 27), 250 (M^+ − 56), 206 (M^+ − 100); $C_{16}H_{19}NO_5$ requires C, 62.94, H, 6.27, N, 4.54 (found C, 63.17, H, 6.35, N, 4.58); ^{1}H NMR ($CDCl_3$) δ 7.42−7.18 (5H, m), 4.72−4.61 (1H, m), 3.20 (1H, dd, J = 13.4, 5.4), 2.82 (2H, d, J = 3.9), 2.78 (1H, dd, J = 13.5, 7.8), 1.56 (9H, s, ^{t}Bu); $[\alpha]^{20}_D$ = −38 (c = 1, CH_2Cl_2).

Reactions of *N*-*tert*-Butyloxycarbonyl *N*-Carboxyanhydrides with Nucleophiles. Reaction with Benzylamine. To a solution of Boc-*β*-alanine NCA **16** (63 mg, 0.29 mmol) in THF (1 mL) was added benzylamine (32 μL, 0.29 mmol). After 10 min, the CO_2 evolution ceased, the reaction was quenched with H_2O (2 mL), and the product was extracted into EtOAc (2 × 5 mL). The organic phases were combined, washed with brine, dried ($MgSO_4$), and evaporated to dryness to afford 63 mg (78%) of the desired product **25** as a white powder: R_f 0.38 (hex/EtOAc, 4:1); mp 121−122 °C; *m*/*z* (ES) 279 (M + H); ^{1}H NMR ($CDCl_3$) δ 7.28−7.39 (5H, m, ArH), 6.03 (1H, br s NH), 5.22 (1H, br s, NH), 4.49 (2H, d, J = 5.7), 3.5 (2H, q, J = 5.6), 2.51 (2H, t, J = 5.8), 1.49 (9H, s, ^{t}Bu).

From the same procedure starting from **17** (54 mg, 0.24 mmol) in THF (1 mL), benzylamine (26 mL, 0.24 mmol) gave **26**. The reaction was stirred overnight until a white precipitate formed; then the reaction was quenched as before to afford 66 mg (96%) of the desired product **26** as a white powder: R_f 0.38 (hex/EtOAc, 4:1); mp 142−143 °C; *m*/*z* (ES) 293 (M + H^+); ^{1}H NMR ($CDCl_3$) 7.26−7.41 (5H, m, ArH), 6.17 (1H, br s NH), 5.19 (1H, br s, NH), 4.48 (2H, d, J = 5.7), 4.03−3.90 (1H, m), 2.48 (2H, dd, J = 5.9, 2.9), 1.44 (9H, s, ^{t}Bu), 1.28 (3H, d, J = 6.7); ν_{max} cm^{-1} (film) 1678, 1528.

Reaction with Benzyl Alcohol. To a solution of Boc-*β*-alanine NCA **16** (32 mg, 0.15 mmol) in THF (1 mL) was added benzyl alcohol (16 μL, 0.29 mmol). After 1 h, the reaction was quenched with H_2O (2 mL) and the product was extracted into EtOAc (3 × 5 mL). The organic phases were combined, washed with brine, dried ($MgSO_4$), and evaporated. Chromatography of the residue using hexane/ethyl acetate (9/1) as eluent yielded the desired product **7**, 29 mg (79%): R_f 0.38 (hex/EtOAc, 4/1); *m*/*z* (ES) M^+ 280; ^{1}H NMR ($CDCl_3$) δ 7.28−7.40 (5H, m, ArH), 5.18 (2H, s, C$H_2C_6H_5$), 5.10 (1H, bs, NH), 3.45 (2H, t, J = 6.0), 2.61 (2H, t, J = 6.0), 1.45 (9H, s, ^{t}Bu**)**.

Reaction with the Lithium Enolate of Ethyl Acetate. To a solution of ethyl acetate (0.1 mL, 1.05 mmol) in THF (1 mL) was added a solution of lithium diisopropyl amide (1.5 mL, solution at 2 mol/L). After 30 min, the solution was added to a cooled solution (−80 °C) of **18** (172 mg, 0.75 mmol) in THF (3 mL). After 2 h, the reaction was quenched with H_2O (5 mL) and the product was extracted into EtOAc (3 × 20 mL). The organic phases were combined, washed with brine, dried ($MgSO_4$), and evaporated. Chromatography of the residue using hexane/ethyl acetate (9:1) as eluent gave the desired product **27**: 110 mg (54%); R_f 0.3 (hex/EtOAc, 4:1); *m*/*z* (ES) 274 (M + H); ^{1}H NMR ($CDCl_3$) δ 4.90 (1H, br m, N*H*), 4.15 (2H, q, J = 7.2, O-CH_2-CH_3), 3.40 (2H, s, CO-CH_2-CO), 3.20 (2H, m, CH-CH_2-NH), 2.9 (1H, m, CH_3-C*H*-CH_2), 1.4 (9H, s, ^{t}Bu), 1.25 (3H, t, J = 7.2, O-CH_2-CH_3), 1.1 (3H, d, J = 7.2, CH-CH_3).

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