An Efficient Synthesis of Optically Active α-(t-Butoxycarbonylamino)-aldehydes from α-Amino Acids

Jean-Alain FEHRENTZ, Bertrand CASTRO

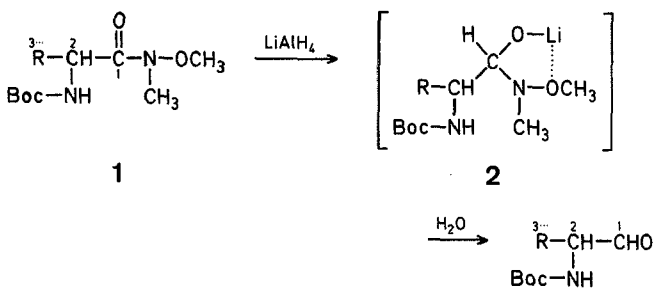
Centre CNRS-INSERM de Pharmacologie-Endocrinologie, Rue de la Cardonille, B.P. 5055, F-34033 Montpellier Cedex

α-(Acylamino)- and α-(alkoxycarbonylamino)-aldehydes are of increasing interest due to their inhibitory properties towards some classes of proteolytic enzymes[1]. Further, they are able to convert the aldehydic carbonyl group into a new chiral center, and they provide an interesting access to numerous unusual amino acids of biological interest. The difficulties generally encountered in the synthesis of functionally substituted aldehydes are particularly serious in the synthesis of α-(acylamino)- and α-(alkoxycarbonylamino)-aldehydes, the main problems arising from the functional and stereochemical instability of these compounds under most reaction conditions. On the other hand, the methods developed for their synthesis should afford high yields and pure products. Chromatographic purification of α-(acylamino)- and α-(alkoxycarbonylamino)-aldehydes is always detrimental and should be avoided.

Aldehydes derived from α-amino acids have hitherto been prepared by oxidation of *N*-protected amino alcohols[2,3,11] or by reduction of amino acids or their esters with diisobutylalu-

minum hydride[4,5]. The products had often to be purified by silica gel chromatography which led to some racemization[6] or had to be used as the crude aldehydes which were contaminated by the corresponding alcohol and unreacted ester.

Our preparation of α-(*t*-butoxycarbonylamino)-aldehydes **(3)** is based on the method of Ref.[7] in which methyl *N*-methylhydroxamates (*N*-methoxy-*N*-methylcarboxamides) are reduced by lithium aluminum hydride. We thus obtained the aldehydes **3** in satisfactory yields and in a hitherto not achieved optical purity. The original method of Ref.[7] prepared the methyl *N*-methylhydroxamates by reaction of simple acyl chlorides with *O,N*-dimethylhydroxylamine. This method was not applicable in our case. We therefore prepared the *N*-methoxy-*N*-methylamides **1** by reaction of the α-(*t*-butoxycarbonylamino) acids with *O,N*-dimethylhydroxylamine hydrochloride in the presence of triethylamine and the coupling reagent benzotriazol-1-yloxytris[dimethylamino]-phosphonium hexafluorophosphate (BOP[10]). Reduction of **1** with lithium aluminum hydride gave the lithium salts **2**; as in the work of Ref.[7], further reduction of the lithium salts is precluded by intramolecular complexation so that the desired aldehydes are obtained upon hydrolysis of the reaction mixtures. The reductions are carried out in diethyl ether at 0 °C using 5 equivalents of lithium aluminum hydride to achieve complete reduction. Only the alanine derivative **1a** which is insufficiently soluble in ether is reduced in tetrahydrofuran. The crude products **3** thus obtained contain only small amounts of impurities which are only detectable by T.L.C. but not in the ^{1}H-N.M.R. spectrum; most of the crude products **3** give satisfactory microanalyses and show high optical rotation.



1 **2** **3**

a R = ^{3}CH$_3$

b R = H$_3$C^5–CH(CH$_3$)^4–CH$_2$^{3}–

c R = H$_3$C^5–CH$_2$^{4}–CH(CH$_3$)^3–

d R = (H$_3$C)$_2$^{3}CH–

e R = C$_6$H$_5$–^{3}CH$_2$–

f R = C$_6$H$_5$–CH$_2$–O–^{3}CH(^{4}CH$_3$)–

[for ^{1}H-N.M.R.: C$_6$H$_5$–C^{a}H^{b}H–]

Column chromatography was carried out on silica gel Merck (0.05–0.2 mm). Thin-layer chromatography (T.L.C.) was carried out on Merck plates precoated with silica gel F 254. Melting points were determined on a Kofler block and are uncorrected. Optical rotations were measured with a Perkin Elmer polarimeter 141 in a 10 cm cell. Microanalyses were performed by the "Service Central de Microanalyses du CNRS". I.R. spectra were recorded using a Perkin Elmer 580 spectrophotometer. ^{1}H-N.M.R. spectra were recorded on a CAMECA 250 MHz spectrometer.

O,N-Dimethylhydroxylamine hydrochloride (98%) was purchased from Aldrich Chemical Co.

***N*-Methoxy-*N*-methyl-α-(*t*-butoxycarbonylamino)-carboxamides (1); General Procedure:**

Triethylamine (1.012 g, 10 mmol) is added to a stirred solution of a Boc-amino acid (10 mmol) in dichloromethane. Then, benzotriazol-1-yloxytris[dimethylamino]-phosphonium hexafluorophosphate (BOP; 3.483 g, 10 mmol) is added, followed after a few minutes by *O,N*-dimethylhydroxylamine hydrochloride (1.117 g, 11 mmol) and triethylamine (1.113 g, 11 mmol). The reaction is monitored by T.L.C. It is complete within 30–60 min, depending on the substrate. If the pH value of the mixture is smaller than 7 the mixture may be neutralized by adding a few drops of triethylamine to allow the reaction to go to completion. The mixture is then diluted with dichloromethane (250 ml) and washed successively with 3 normal hydrochloric acid (3 × 30 ml), saturated sodium hydrogen carbonate solution (3 × 30 ml), and saturated sodium chloride solution (3 × 30 ml). The organic solution is dried with magnesium sulfate and the solvent evaporated. The residual crude product **1** is purified by chromatography on silica gel or by crystallization to remove traces of *N,N*-dimethylamide produced by an impurity in the commercial *O,N*-dimethylhydroxylamine hydrochloride.

N$^\alpha$-(t-*Butoxycarbonyl*)-L-*alanine* N-*Methoxy*-N-*methylamide* **(1a);** yield: 85%; m.p. 150 °C (ethyl acetate); R_f: 0.29 (ethyl acetate/hexane 1/1), 0.16 (ethyl acetate/hexane 1/2).

$C_{10}H_{20}N_2O_4$	calc.	C 51.71	H 8.68	N 12.06
(232.3)	found	51.46	8.80	11.87

I.R. (NaCl): ν = 3287, 2940, 1706, 1660, 1502, 1391 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 5.35 (d, 1H, NH, $J_{NH,2}$ = 7.5 Hz); 4.70 (dq, 1H, 2-H, $J_{2,NH}$ = 7.5 Hz, $J_{2,3}$ = 7 Hz); 3.78 (s, 3H, OCH_3); 3.22 (s, 3H, N—CH_3); 1.45 [s, 9H, $C(CH_3)_3$]; 1.32 ppm (d, 3H, 3,3,3-H_3, $J_{3,2}$ = 7 Hz).

N$^\alpha$-(t-*Butoxycarbonyl*)-L-*leucine* N-*Methoxy*-N-*methylamide* **(1b);** yield: 94%; oil; R_f: 0.39 (ethyl acetate/hexane 1/1), 0.27 (ethyl acetate/hexane 1/2).

$C_{13}H_{26}N_2O_4$	calc.	C 56.92	H 9.55	N 10.21
(274.4)	found	56.64	9.53	10.40

I.R. (film): ν = 3325, 2935, 1710, 1660, 1500, 1393 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 5.32 (d, 1H, NH, $J_{NH,2}$ = 7.5 Hz); 4.73 (dt, 1H, 2-H, $J_{2,NH}$ = 7.5 Hz); 3.79 (s, 3H, OCH_3); 3.19 (s, 3H, N—CH_3); 1.81–1.65 (m, 1H, 4-H); 1.52–1.30 (m, 2H, 3-H); 1.44 [s, 9H, $C(CH_3)_3$]; 0.95 ppm [2d, 6H, $CH(CH_3)_2$, $J_{CH_3,4}$ = 6.5 Hz].

N$^\alpha$-(t-*Butoxycarbonyl*)-L-*isoleucine* N-*Methoxy*-N-*methylamide* **(1c);** yield: 70%; oil; R_f: 0.37 (ethyl acetate/hexane 1/1), 0.25 (ethyl acetate/hexane 1/2).

$C_{13}H_{26}N_2O_4$	calc.	C 56.92	H 9.55	N 10.21
(274.4)	found	56.77	9.46	10.16

I.R. (film): ν = 3340, 3325, 2940, 1712, 1660, 1500, 1390 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 5.50 (d, 1H, NH, $J_{NH,2}$ = 9.5 Hz); 4.62 (dd, 1H, 2-H, $J_{2,NH}$ = 9.5 Hz); 3.78 (s, 3H, OCH_3); 3.20 (s, 3H, N—CH_3); 1.74 (m, 1H, 3-H); 1.42 [s, 9H, $C(CH_3)_3$]; 1.22–1.01 (m, 2H, 4-H); 0.90 (d, 3H, 3-CH_3, $J_{CH_3,3}$ = 7 Hz); 0.88 ppm (t, 3H, 5,5,5-H_3, $J_{5,4}$ = 7 Hz).

N$^\alpha$-(t-*Butoxycarbonyl*)-L-*valine* N-*Methoxy*-N-*methylamide* **(1d);** yield: 80%; oil; R_f: 0.41 (ethyl acetate/hexane 1/1), 0.29 (ethyl acetate/hexane 1/2).

$C_{12}H_{24}N_2O_4$	calc.	C 55.36	H 9.29	N 10.76
(260.3)	found	55.33	9.33	10.58

I.R. (film): ν = 3330, 2940, 1712, 1660, 1500, 1390 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 5.21 (d, 1H, NH, $J_{NH,2}$ = 9 Hz); 4.58 (dd, 1H, 2-H, $J_{2,3}$ = 7 Hz); 3.78 (s, 3H, OCH_3); 3.22 (s, 3H, N—CH_3); 1.99 (m, 1H, 3-H); 1.44 [s, 9H, $C(CH_3)_3$]; 0.96 (d, 3H, 4,4,4-H_3, $J_{4,3\text{-}CH_3}$ = 7 Hz); 0.91 ppm (d, 3H, 3-CH_3, $J_{3\text{-}CH_3,4}$ = 7 Hz).

N$^\alpha$-(t-*Butoxycarbonyl*)-L-*phenylalanine* N-*Methoxy*-N-*methylamide* **(1e);** yield: 95%; oil; R_f: 0.37 (ethyl acetate/hexane 1/1), 0.22 (ethyl acetate/hexane 1/2).

$C_{16}H_{24}N_2O_4$	calc.	C 62.32	H 7.84	N 9.08
(308.4)	found	61.26	7.78	9.05

I.R. (film): ν = 3325, 2937, 1712, 1662, 1495, 1390 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 7.6 (m, 5H, C_6H_5); 5.68 (d, 1H, NH,

$J_{NH,2}$ = 8.5 Hz); 4.95 (ddd, 1 H, 2-H, $J_{2,H^a} = J_{2,H^b}$ = 6 Hz); 3.60 (s, 3 H, OCH_3); 3.10 (s, 3 H, N—CH_3); 3.05 (dd, 1 H, 3-H^a, J_{H^a,H^b} = 13.5 Hz); 2.87 (dd, 1 H, 3-H^b); 1.38 ppm [s, 9 H, $C(CH_3)_3$].

N^{α}-(t-Butoxycarbonyl)-O-benzyl-L-threonine N-Methoxy-N-methylamide **(1f);** yield: 95%; oil; R_f: 0.38 (ethyl acetate/hexane 1/1), 0.23 (ethyl acetate/hexane 1/2).

$C_{18}H_{28}N_2O_5$	calc.	C 61.34	H 8.01	N 7.95
(352.4)	found	61.21	8.05	7.53

I.R. (film): ν = 3440, 3330, 2935, 1715, 1670, 1495, 1390 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 7.3 (m, 5 H, C_6H_5); 5.52 (d, 1 H, NH, $J_{NH,2}$ = 9 Hz); 4.62 (dd, 1 H, 2-H, $J_{2,3}$ = 3 Hz); 4.54 (d, 1 H, H^a, J_{H^a,H^b} = 12 Hz); 4.40 (d, 1 H, H^b); 3.89 (dq, 1 H, 3—H, $J_{3,4}$ = 5.5 Hz); 3.63 (s, 3 H, OCH_3); 3.11 (s, 3 H, N—CH_3); 1.44 [s, 9 H, $C(CH_3)_3$]; 1.24 ppm (d, 3 H, 4,4,4-H_3).

α-(t-Butoxycarbonylamino)-aldehydes (3); General Procedure:
Lithium aluminum hydride (95 mg, 2.5 mmol, 5 equiv) is added to a stirred solution of an *N*-methoxy-*N*-methyl-α-(*t*-butoxycarbonylamino)-carboxamide (**1**; 2 mmol) in ether (20 ml) (for the reduction of amide **1a**, tetrahydrofuran is used instead). Reduction is complete within 15–20 min. The mixture is hydrolyzed with a solution of potassium hydrogen sulfate (477 mg, 3.5 mmol) in water (10 ml). Then, ether (50 ml) is added; the aqueous phase is separated and extracted with ether (3 × 50 ml). The organic phases are combined, washed with 3 normal hydrochloric acid (3 × 20 ml), saturated sodium hydrogen carbonate solution (3 × 20 ml), and saturated sodium chloride solution (3 × 20 ml), and dried with magnesium sulfate. The solvent is evaporated to leave product **3** which, according to T.L.C. analysis, contains only small amounts of impurities. The aldehydes **3** can be stored under argon for ~2 weeks. When stored in organic solvents at room temperature, aldehydes **3** undergo slow decomposition.

N-(t-Butoxycarbonyl)-L-alaninal **(3a);** yield: 88%; m.p. 88–89 °C; R_f: 0.44 (ethyl acetate/hexane 1/1), 0.28 (ethyl acetate/hexane 1/2); $[\alpha]_D^{20}$: +36.7° (*c* 1, CH_2Cl_2), −34.1° (*c* 1, methanol) (Ref.[9], $[\alpha]_D^{20}$: +1.0°, *c* 1, CH_2Cl_2].

$C_8H_{15}NO_3$	calc.	C 55.47	H 8.73	N 8.08
(173.2)	found	55.29	8.85	8.07

I.R. (NaCl): ν = 3440, 2935, 2720, 1740, 1720, 1500, 1395 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 9.58 (s, 1 H, 1-H); 5.46 (d, 1 H, NH, $J_{NH,2}$ = 7 Hz); 4.2 (dq, 1 H, 2-H, $J_{2,3}$ = 7 Hz); 1.45 [s, 9 H, $C(CH_3)_3$]; 1.33 ppm (d, 3 H, 3,3,3-H_3).

N-(t-Butoxycarbonyl)-L-leucinal **(3b);** yield: 96%; m.p. 63–66 °C; R_f: 0.58 (ethyl acetate/hexane 1/1), 0.45 (ethyl acetate/hexane 1/2); $[\alpha]_D^{20}$: +11° (*c* 1, CH_2Cl_2), −45,7° (*c* 1, methanol) (Ref.[11], $[\alpha]_D^{20}$: −42.3°, *c* 1, methanol).

$C_{11}H_{21}NO_3$	calc.	C 61.14	H 9.83	N 6.51
(215.3)	found	60.22	9.77	6.72

I.R. (NaCl): ν = 3350, 2940, 2725, 1740, 1720, 1510, 1395 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 9.6 (s, 1 H, 1-H); 5.48 (d, 1 H, NH, $J_{NH,2}$ = 7 Hz); 4.2 (m, 1 H, 2-H); 1.9–1.45 (m, 3 H, 3,3-H_2, 4-H); 1.45 [s, 9 H, $C(CH_3)_3$]; 0.96 ppm [d, 6 H, $CH(CH_3)_2$, $J_{CH_3,4}$ = 6.5 Hz).

N-(t-Butoxycarbonyl)-L-isoleucinal **(3c);** yield: 90%; oil; R_f: 0.58 (ethyl acetate/hexane 1/1), 0.42 (ethyl acetate/hexane 1/2); $[\alpha]_D^{20}$: +0.92.8° (*c* 1, CH_2Cl_2), −24.4° (*c* 1, methanol).

$C_{11}H_{21}NO_3$	calc.	C 61.14	H 9.83	N 6.51
(215.3)	found	60.34	9.57	6.53

I.R. (film): ν = 3350, 2940, 2720, 1730, 1710, 1510, 1395 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 9.68 (s, 1 H, 1-H); 5.34 (d, 1 H, NH, $J_{NH,2}$ = 7 Hz); 4.28 (dd, 1 H, 2-H, $J_{2,3}$ = 5 Hz); 2.12–1.92 (m, 1 H, 3-H); 1.42 [s, 9 H, $C(CH_3)_3$]; 1.2–1.0 (m, 2 H, 4,4-H_2); 0.99 (d, 3 H, 3-CH_3, $J_{CH_3,3}$ = 7 Hz); 0.95 ppm (t, 3 H, 5,5,5-H_3, $J_{5,4}$ = 7 Hz).

N-(t-Butoxycarbonyl)-L-valinal **(3d);** yield: 93%; oil; R_f: 0.61 (ethyl acetate/hexane 1/1), 0.50 (ethyl acetate/hexane 1/2); $[\alpha]_D^{20}$: +82.1° (*c* 1, CH_2Cl_2), −19° (*c* 1, methanol) (Ref.[9], $[\alpha]_D^{20}$: +1.2 (*c* 1, CH_2Cl_2). All data refer to the crude oily product which cannot be chromatographed.

$C_{10}H_{19}NO_3$	calc.	C 59.68	H 9.51	N 6.96
(201.3)	found	59.28	9.46	7.29

I.R. (film): ν = 2940, 2725, 1740, 1500, 1390 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 9.66 (s, 1 H, 1-H); 5.33 (d, 1 H, NH, $J_{NH,2}$ = 7 Hz); 4.23 (dd, 1 H, 2-H); 2.29 (m, 1 H, 3-H); 1.46 [s, 9 H, $C(CH_3)_3$]; 0.99 ppm [2 d, 6 H, $CH(CH_3)_2$, $J_{CH_3,3}$ = 7 Hz).

N-(t-Butoxycarbonyl)-L-phenylalaninal **(3e);** yield: 86%; m.p. 86 °C; R_f: 0.50 (ethyl acetate/hexane 1/1), 0.34 (ethyl acetate/hexane 1/2); $[\alpha]_D^{20}$: +40.4° (*c* 1, CH_2Cl_2), −44.4° (*c* 1, methanol) (Ref.[9], $[\alpha]_D^{20}$: +2.9°, *c* 1, CH_2Cl_2).

$C_{14}H_{19}NO_3$	calc.	C 67.45	H 7.68	N 5.62
(249.3)	found	67.33	7.54	5.81

I.R. (NaCl): ν = 3435, 2940, 2760, 2730, 1740, 1725, 1500, 1395, 1240 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 9.59 (s, 1 H, 1-H); 7.22 (m, 5 H, C_6H_5); 5.22 (d, 1 H, NH, $J_{NH,2}$ = 6.5 Hz); 4.38 (ddd, 1 H, 2-H, $J_{2,H^a} = J_{2,H^b}$ = 6 Hz); 3.61 (dd, 1 H, 3-H^a, J_{H^a,H^b} = 14 Hz); 3.53 (dd, 1 H, 3-H^b); 1.42 ppm [s, 9 H, $C(CH_3)_3$].

N-(t-Butoxycarbonyl)-O-benzyl-L-threoninal **(3f);** yield: 95%; oil; R_f: 0.53 (ethyl acetate/hexane 1/1), 0.42 (ethyl acetate/hexane 1/2); $[\alpha]_D^{20}$: +10.8° (*c* 1, CH_2Cl_2), +16° (*c* 1, methanol) (Ref.[9], $[\alpha]_D^{20}$: +1.4°, *c* 1, CH_2Cl_2). All data refer to the crude oily product which cannot be chromatographed.

$C_{16}H_{23}NO_4$	calc.	C 65.55	H 7.90	N 4.77
(293.4)	found	64.82	7.89	4.81

I.R. (film): ν = 3440, 2940, 2750, 1750, 1725, 1500, 1390 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 9.60 (s, 1 H, 1-H); 7.3 (m, 5 H, C_6H_5); 5.40 (d, 1 H, NH, $J_{NH,2}$ = 7.5 Hz); 4.57 (d, 1 H, H^a, J_{H^a,H^b} = 11.5 Hz); 4.40 (d, 1 H, H^b); 4.25 (m, 2 H, 2-H, 3-H); 1.46 [s, 9 H, $C(CH_3)_3$]; 1.25 ppm (d, 3 H, 4,4,4-H_3, $J_{4,3}$ = 6.5 Hz).

Received: December 2, 1982
(Revised form: February 7, 1983)

1 H. Umezawa, *Enzyme Inhibitors of Microbial Origin*, University Park Press, Baltimore, Md, 1972.
2 R. C. Thompson, *Biochemistry* **12,** 47 (1973).
3 K. Kawamura, S. Kondo, K. Maeda, H. Umezawa, *Chem. Pharm. Bull.* **17,** 1902 (1969).
4 A. Ito, R. Takahashi, Y. Baba, *Chem. Pharm. Bull.* **23,** 3081 (1975).
5 R. Kanazawa, T. Tokorayama, *Synth. Commun.* **1976,** 526.
6 The aldehyde derived from D-alanine has been prepared by reduction of the 3,5-dimethylpyrazolide of *N*-(*t*-butoxycarbonyl)-D-alanine with lithium aluminum hydride in tetrahydrofuran at −20 °C: S. Tokita, Y. Umezawa et al., *Tetrahedron Lett.* **23,** 521 (1982).
7 S. Nahm, S. Weinreb, *Tetrahedron Lett.* **22,** 3815 (1981).
8 D. H. Rich, E. T. Sun, A. S. Boparai, *J. Org. Chem.* **43,** 3624 (1978).
9 C. F. Stanfield, J. E. Parker, P. Kanellis, *J. Org. Chem.* **46,** 4797 (1981).
10 B. Castro et al., *Tetrahedron Lett.* **1975,** 1219; *Synthesis* **1976,** 751; *J. Chem. Res.* [S] **1977,** 182; *Tetrahedron Lett.* **1979,** 3321.
11 K. E. Rittle, C. F. Homnick, G. S. Ponticello, B. E. Evans, *J. Org. Chem.* **47,** 3016 (1982).