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A New Method to synthesize α-Aminoaldehydes[1]

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Benzyloxycarbonyl (Cbz)-amino acid esters were reduced to the corresponding α-aminoaldehydes with diisobutylaluminum hydride. Comparison of specific rotation of the Cbz-aminoalcohols, which were derived from the aldehydes by sodium borohydride reduction, with that of the optically pure material showed that chromatography on a silica gel caused marked racemization in the Cbz-α-aminoaldehyde through keto-enol tautomerism. Cbz-S-Bzl-cysteinal was liable to racemize to a great extent. On the other hand, little racemization occurred in Cbz-N^G-nitroargininal. This fact might be accounted for the characteristic cyclic carbinolamine structure of the argininal derivative.

The semicarbazones prepared from the crude Cbz-α-aminoaldehydes could be reproduced to the initial aldehydes without racemization. These semicarbazones might be used as good starting materials in peptide aldehyde synthesis.

Recently, Umezawa, *et al.* isolated various proteinase inhibitors such as leupeptin, chymostatin, antipain and elastational from cultured broths of various species of Actinomycetes.[3] The structures of these proteinase inhibitors were identified also by these authors to be peptide derivatives which possessed aminoaldehyde residues in C-terminal parts.[4]

One of the most proper ways to synthesize chemically these interesting peptide aldehydes is a stepwise elongation of peptide moiety starting from C-terminal α-aminoaldehyde. To data the preparations of optically active α-aminoaldehydes from corresponding α-amino acid derivatives have been reported by various investigators as described below: (a) reduction of α-amino acid esters with sodium amalgam,[5] (b) Rosenmund reduction of N-phthalylamino acid chlorides,[6] (c) lithium aluminum hydride reduction of tosylated α-aminoacyldimethylpyrazoles,[7] (d) lithium aluminum hydride reduction of benzyloxycarbonyl (Cbz)-α-aminoacylimidazoles,[8] (e) catalytic reduction of mixed carbonic-carboxylic acid anhydrides prepared from acylated α-amino acids.[9]

1) Amino acids and their derivatives are of the L-configuration. Abbreviations used are those recommended by IUPAC-IUB Commission on Biochemical Nomenclature: *Biochemistry*, **5**, 2485 (1966); *ibid.*, **6**, 362 (1967); *ibid.*, **11**, 1726 (1972).
2) Location: *1-2-58, Hiromachi Shinagawa-ku, Tokyo.*
3) T. Aoyagi, T. Takeuchi, A. Matsuzaki, K. Kawamura, S. Kondo, M. Hamada, K. Maeda, and H. Umezawa, *J. Antibiotics* (Tokyo), **22**, 283 (1969); H. Umezawa, T. Aoyagi, H. Morishima, S. Kunimoto, M. Matsuzaki, M. Hamada, and T. Takeuchi, *ibid.*, **23**, 425 (1970); H. Suda, T. Aoyagi, M. Hamada, T. Takeuchi, and H. Umezawa, *ibid.*, **25**, 263 (1972); H. Umezawa, T. Aoyagi, A. Okura, H. Morishima, T. Takeuchi, and Y. Okami, *ibid.*, **26**, 787 (1973).
4) K. Kawamura, S. Kondo, K. Maeda, and H. Umezawa, *Chem. Pharm. Bull.* (Tokyo), **17**, 1902 (1969); K. Tatsuta, N. Mikami, K. Fujimoto, S. Umezawa, H. Umezawa, and T. Aoyagi, *J. Antibiotics* (Tokyo), **26**, 625 (1973); S. Umezawa, K. Tatsuta, K. Fujimoto, T. Tsuchiya, H. Umezawa, and H. Naganawa, *ibid.*, **25**, 267 (1972).
5) E. Adams, *J. Biol. Chem.*, **217**, 317 (1955).
6) K. Balenović, N. Bregant, D. Cerar, D. Fleš, and I. Jambrešić, *J. Org. Chem.*, **18**, 297 (1953); K. Balenović, N. Bregant, T. Galijan, Z. Štefanac, and V. Škarić, *ibid.*, **21**, 115 (1956).
7) W. Ried and P. Paender, *Ann.*, **640**, 111 (1961).
8) B. Shimizu, A. Saito, A. Ito, K. Tokawa, K. Maeda, and H. Umezawa, *J. Antibiotics* (Tokyo), **25**, 515 (1972).
9) H. Seki, K. Koga, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **20**, 361 (1972).

However, various disadvantages were pointed out in these methods. In (a) and (c), the yields were not always satisfactory and in (b) the use of phthalyl group was not convenient for the present purpose, because hydrazine hydrate, a sensitive reagent for aldehyde group, should be applied in the removal of phthalyl group. Cbz-α-aminoacylimidazoles, the starting materials of (d), were easily decomposed by moisture and poor reproducibilities in yields were observed in (e). In this paper the present authors describe another approach to synthesize optically pure α-aminoaldehydes starting from common α-amino acids.

Table I. Physical Constants and Elemental Analysis of Cbz-Amino Acid Esters

Compound	Method[a]	Yield (%)	$[\alpha]_D^{20}$ (c, solvent)	Formula	Analysis (%) Found (Calcd.) C	H	N
Cbz-N^G-Nitroarg-OMe	A	87	−11.2(1.0, DMF)	$C_{15}H_{21}O_6N_5$	49.31 (49.04)	5.54 (5.76)	19.06 (19.07)
Cbz-Leu-OEt	A	80	−27.5(1.0, MeOH)	$C_{16}H_{23}O_4N$	65.75 (65.51)	7.87 (7.90)	4.68 (4.78)
Cbz-Phe-OEt	A	88	−10.1(1.4, EtOH)	$C_{19}H_{21}O_4N$	69.31 (69.70)	6.41 (6.47)	4.16 (4.28)
Cbz-S-Bzl-Cys-OEt	A	85	−53.4(1.6, MeOH)	$C_{20}H_{23}O_4NS$	64.28 (64.32)	6.22 (6.21)	3.63 (3.75)
Cbz-Trp-OMe	A	84	−11.4(1.1, MeOH)	$C_{20}H_{20}O_4N_2$	67.98 (68.17)	5.90 (5.72)	8.17 (7.95)
Cbz-Ile-OMe	B	90	−11.5(1.1, MeOH)	$C_{15}H_{21}O_4N$	64.74 (64.49)	7.78 (7.58)	5.06 (5.01)
Cbz-Pro-OMe	B	96	−57.3(1.0, MeOH)	$C_{14}H_{17}O_4N$	64.00 (63.86)	6.47 (6.51)	5.08 (5.32)
Cbz-Met-OMe	B	93	−34.1(1.1, MeOH)	$C_{14}H_{19}O_4NS$	56.41 (56.54)	6.42 (6.44)	4.67 (4.71)
Cbz-N$^\varepsilon$-Cbz-Lys-OMe	B	95	−13.0(1.1, MeOH)	$C_{23}H_{28}O_6N_2$	64.29 (64.47)	6.72 (6.59)	6.62 (6.54)
Cbz-Ala-OMe	B	93	−34.2(1.1, MeOH)	$C_{12}H_{15}O_4N$	60.37 (60.75)	6.47 (6.37)	5.86 (5.90)

a) Details are described in the text.
A: benzyloxycarbonylation of amino acid esters
B: esterification of Cbz-amino acids with diazomethane

Zakharkin, *et al.* reported that diisobutylaluminum hydride [(i-Bu)$_2$AlH] was an effective reagent for a conversion of a carboxylic acid ester into the corresponding aldehyde in *n*-hexane or toluene at −70°.[10] We applied this reducing agent for the preparation of a Cbz-α-aminoaldehyde from the corresponding Cbz-α-amino acid ester. The Cbz-α-amino acid methyl or ethyl esters were reduced with 2—4 molar equivalents of (i-Bu)$_2$AlH in anhydrous toluene at −50° in a stream of dry argon gas for 60 min to give the Cbz-α-aminoaldehydes as expected with a small amount of the corresponding amino alcohol derivatives probably produced by a further reduction of the desired aldehydes. In the case of toluene insoluble material (*e.g.* Cbz-N^G-nitroarginine methyl ester), anhydrous tetrahydrofuran was applied successfully. The resulted Cbz-α-aminoaldehydes were usually very difficult to be purified without chromatographical separation of the reaction mixtures. In several preparations of the α-aminoaldehyde derivatives, we attempted column chromatography on silica gel eluted with chloroform containing small amount of methanol. Some of the Cbz-α-aminoaldehydes thus purified, however, were found to show unexpectedly low specific rotations (Table II). It is possible that α-aminoaldehydes produced are racemized through keto-enol tautomerism during the reduction and/or in the purification stage. Therefore, we estimated the extent of possible racemization after

10) L.I. Zakharkin and I.M. Khorlina, *Tetrahedron Letters*, **1962**, 619.

TABLE II. Cbz-α-Aminoaldehydes Purified by Silica Gel Chromatography

Cbz-α-Aminoaldehyde	*Rf* value[a]	$[\alpha]_D^t$ (c, MeOH)	Yield (%)	2,4-Dinitrophenylhydrazone mp (°C)	Formula	Analysis (%) Found (Calcd.) C	H	N
N^G-Nitroargininal	0.21[1]	-1.4^{21}(2.1)	21	119—123	$C_{20}H_{23}O_8N_9$	46.32 (46.42)	4.64 (4.48)	24.24 (24.36)
Leucinal	0.49[2]	-3.6^{22}(1.4)	48	100—102	$C_{20}H_{23}O_6N_5$	56.15 (55.94)	5.57 (5.40)	16.31 (16.31)
Phenylalaninal	0.30[2]	-2.7^{21}(2.3)	55	179—181	$C_{23}H_{21}O_6N_5$	59.78 (59.60)	4.56 (4.57)	15.00 (15.11)
S-Bzl-cysteinal	0.31[2]	-0.1^{21}(1.7)	68	106—108	$C_{24}H_{23}O_6N_5S$	56.49 (56.57)	4.50 (4.55)	13.92 (13.75)
Tryptophanal	0.15[2]	-3.3^{21}(1.1)	33	90— 94	$C_{25}H_{22}O_6N_6$	59.47 (59.75)	4.42 (4.41)	16.82 (16.73)
Isoleucinal	0.48[2]	$+2.3^{22}$(1.2)	59	122—125	$C_{20}H_{23}O_6N_5$	56.04 (55.94)	5.38 (5.40)	16.26 (16.31)
Prolinal	0.14[2]	-40.8^{21}(1.9)	64	109—114	$C_{19}H_{19}O_6N_5$	54.93 (55.20)	4.89 (4.63)	16.84 (16.94)
Methioninal	0.16[2]	-7.4^{21}(2.1)	61	128—130	$C_{19}H_{21}O_6N_5S$	50.60 (51.00)	4.75 (4.73)	15.42 (15.65)
N^ε-Cbz-lysinal	0.10[2]	-9.1^{21}(1.2)	53	120—122	$C_{28}H_{20}O_8N_6 \cdot 1/2EtOH$	57.70 (57.89)	5.26 (5.53)	14.28 (13.97)
Alaninal	0.13[2]	-1.2^{22}(1.6)	50	185—187	$C_{17}H_{17}O_6N_5$	52.67 (52.71)	4.47 (4.42)	18.08 (18.08)
O-Bu^t-threoninal	0.29[2]	$+6.3^{22}$(1.0)	53	122—127	$C_{22}H_{27}O_7N_5$	56.10 (55.80)	5.93 (5.75)	14.79 (14.79)

a) *Rf* values refer to the following solvent systems; 1: $CHCl_3$–MeOH (10: 1), 2: $CHCl_3$–MeOH (100: 1)

the reduction and the chromatographical purification, respectively. Thus, the reaction mixture was further reduced with sodium borohydride ($NaBH_4$). The comparison of specific rotations with the authentic optically pure materials revealed that the racemization scarcely occurs during the reaction, but that chromatographical purification of Cbz-α-aminoaldehyde results in considerable racemization. Saeki, *et al.* reported that the adsorption of some D-glyceroaldehyde on silica gel induced an epimerization of its 6-position, giving the L-isomer.[11]

The degree of racemization during chromatography varies with the structure of Cbz-α-aminoaldehyde. Longer adsorption of the Cbz-α-aminoaldehydes on silica gel column appears to cause more racemization. These results are shown in Table III. Then we attempted to purify the aldehydes as their semicarbazones, in which keto-enol tautomerism is suppressed. The reaction mixture was directly treated with semicarbazide. Cbz-α-aminoaldehyde semicarbazone thus obtained was purified by silica gel chromatography and treated with formalin and hydrochloric acid to regenerate the Cbz-α-aminoaldehyde, which was immediately reduced to the corresponding aminoalcohol with $NaBH_4$. The optical rotation of the resulted Cbz-aminoalcohol showed that little racemization had taken place during chromatography when the aldehyde was protected as semicarbazone (Table III). Therefore, these Cbz-α-aminoaldehyde semicarbazones may be suitable as starting materials in the chemical synthesis of peptide aldehydes. The attempts will be reported in our forthcoming paper.

As shown in Table III, the order of the extent of the racemization in Cbz-α-aminoaldehydes on silica gel was as follows: Cbz-S-Bzl-cysteinal$\gg$Cbz-phenylalaninal$>$Cbz-leucinal$\gg$Cbz-N^G-nitroargininal. It is especially interesting to note that the order of the extent of the racemization was similar to that observed by Bodanszky, *et al.* during the base-catalyzed race-

11) H. Saeki and E. Ohki, *Chem. Pharm. Bull.* (Tokyo), **18**, 789 (1970).

Table III. Degree of Recemization (%) of Cbz-α-Aminoaldehydes

Compound	After the purification by silica gel chromatography[a] Exposure time			After the purification as their semicarbazones[a]
	0 hr	6 hr	22 hr	
Cbz-N^G-nitroargininal	0%	5%	9%	0%
Cbz-leucinal	0%	32%	65%	0%
Cbz-phenylalaninal	0%	53%	85%	0%
Cbz-S-Bzl-cysteinal	7%	99%	100%	5%

a) Details are described in the text.

Table IV. Physical Constants and Elemental Analysis of Optically Pure Cbz-aminoalcohol

Compound	mp (°C)	$[\alpha]_D^t$ (c, solvent)	Analaysis (%) Calcd. C	H	N	Found C	H	N
Cbz-N^G-nitroargininol	134—137	-17.8^{19} (1.5, DMF)	49.55	6.24	20.64	49.72	6.07	20.74
Cbz-leucinol	34— 35	$-26.9^{20.5}$ (1.2, EtOH)	66.90	8.42	5.57	66.98	8.45	5.63
Cbz-phenylalaninol	90— 92	-41.5^{20} (1.4, EtOH)	71.56	6.71	4.91	71.48	6.81	4.92
Cbz-S-Bzl-cysteinol	61— 63	-34.3^{21} (1.0, EtOH)	65.22	6.39	4.23	65.06	6.47	4.09

mization of Cbz-amino acid p-nitrophenyl ester.[12] Liberek also obtained similar results in base-catalyzed racemization of Cbz-amino acid active derivatives.[13] These facts were accounted for by proton-abstraction on the α-carbon atom which was facilitated by stabilization of the resulting anion.

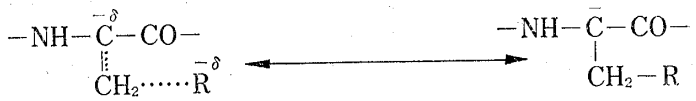

Chart 1

In such Cbz-α-aminoaldehydes that a group capable of involving a type of conjugation with the enolate form is present at the β-position, racemization at the contact with silica gel (Lewis acid) will readily occur.

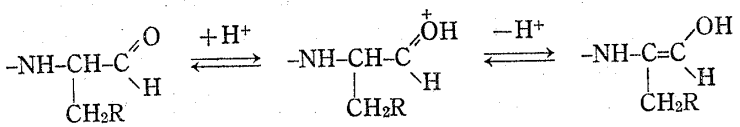

Chart 2

The limited racemization of Cbz-N^G-nitroargininal seems to be related to its non-carbonyl structure. Shimizu, *et al.* reported that the infrared and nuclear magnetic resonance spectra of Cbz-N^G-nitroargininal indicate the cyclized carbinolamine structure as shown below instead of the presence of a free aldehyde group.[8] This cyclic structure probably prevented the nitroargininal derivative from racemization based on keto-enol tautomerism.

12) M. Bodanszky and C.A. Birkhimer, *Chimia* (Aarau), **14**, 366 (1960).
13) B. Liberek, *Tetrahedron Letters*, **1963**, 925.

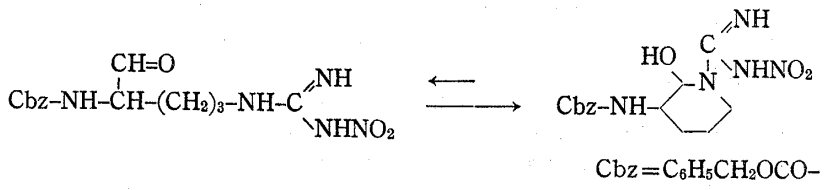

Chart 3

Experimental

Melting points are not corrected. Thin-layer chromatography (TLC) was performed on silica gel (Kieselgel G, Merk). Optical rotations were measured by a Perkin Elmer 141 automatic polarimeter in 1 dm tubes. For column chromatography, Silica Gel (B) (Iwai Kagaku Co., Ltd.) was used. $(i\text{-Bu})_2AlH$ was obtained from Mitsuwa's Pure Chemicals, as *n*-hexane solution. $NaBH_4$ was purchased from Teika Sangyo Co., Ltd. Toluene was distilled and dried over sodium wire. Tetrahydrofuran (THF) was stored over sodium wire after distillation over lithium aluminum hydride.

Synthesis of Cbz-Amino Acid Esters——The physical data are described in Table I.

A) Benzyloxycarbonylation of Amino Acid Esters: To an ice-cooled suspension of amino acid ester hydrochloride (30 mmoles) and potassium bicarbonate (120—180 mmoles) in H_2O (120 ml) and AcOEt (150 ml), Cbz-chloride (36 mmoles) was added with vigorous stirring over a period of 30 min. After stirring for 1 hr, the aqueous layer was acidified with 1N HCl. The organic layer was separated, washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo* to give a crystalline mass. Recrystallization was carried out from AcOEt or ether-pet. ether. If the product was not crystallized, the oil was purified by chromatography on silica gel (100—150 g) using benzene–*n*-hexane (1: 1, v/v) as eluent.

B) Esterification of Cbz-Amino Acids with Diazomethane: To an ice-cooled solution of Cbz-amino acid (20 mmoles) in ether (70 ml), 1.5—2.0 molar equivalents of diazomethane solution in ether (50—70 ml) was added with stirring over a period of 30 min. After the resulting mixture was allowed to stand for 3 hr at room temperature, the solvent was evaporated *in vacuo*. The residue was purified by chromatography on silica gel (100—150 g) eluted with benzene if necessary.

Cbz-Thr(Bu^t)-OMe: The title compound was prepared by the method of Schroeder.[14]

General Procedure for the Synthesis of Cbz-α-Aminoaldehydes with the Exception of Cbz-N^G-Nitroargininal——To a solution of Cbz-amino acid ester (19 mmoles) in anhyd. toluene (100 ml) cooled to about −50° in a dry-ice-acetone bath, 1.76M $(i\text{-Bu})_2AlH$ solution (22 ml) in *n*-hexane was added dropwise over a period of 30 min, with vigorous stirring, in the stream of dry argon. After stirring for an additional 20 min, excess reagent was decomposed by careful addition of 2N HCl (100 ml). The resulting reaction mixture was allowed to warm to approximately 0° and the organic layer was separated. The aqueous layer was extracted twice with AcOEt (60 ml). The organic layers were combined, washed with H_2O, dried over Na_2SO_4 and then evaporated to dryness below 40° (bath temp.). The residue was purified by chromatography on silica gel (100—200 g) eluted with $CHCl_3$. The starting Cbz-amino acid ester was eluted ahead of the desired Cbz-α-aminoaldehyde which was characterized as its 2,4-dinitrophenylhydrazone (Table II). In the case of Cbz-O-Bu^t-threoninal and Cbz-tryptophanal, 10% citric acid was used for decomposition of excess $(i\text{-Bu})_2AlH$.

Cbz-N^G-Nitroargininal: To a stirred solution of Cbz-N^G-nitroarginine methyl ester (8.0 g, 22 mmoles) in anhyd. THF (200 ml) keeping the temperature at about −25°, 1.76M $(i\text{-Bu})_2AlH$ solution (50 ml) in *n*-hexane was added over a period of 1 hr under dry argon atmosphere. Stirring was continued for an additional 30 min at the same temperature. After decomposition of excess reagent by addition of 2N HCl (200 ml), the reaction mixture was stirred with AcOEt (400 ml) for about 20 min at room temperature. The organic layer was separated, washed with H_2O, dried over Na_2SO_4 and concentrated *in vacuo* below 40° (bath temp.). The residue (7.3 g) was applied on a column of silica gel (90 g) and the column was eluted with $CHCl_3$–MeOH (100:3, v/v) to give three fractions. The first fraction was Cbz-N^G-nitroarginine methyl ester (2.6 g), starting material. The second fraction giving a positive 2,4-dinitrophenylhydrazine test was evaporated *in vacuo* below 40° (bath temp.). The residue (2.7 g) was dissolved in 70% EtOH (20 ml) and treated with semicarbazide hydrochloride (0.9 g) and sodium acetate (1.4 g) at 80° for 5 min. On cooling to room temperature, an oily substance was deposited. Trituration with EtOH and recrystallization from EtOH gave a crystalline powder (2.0 g), mp 105—108°. This compound was identified as Cbz-N^G-nitroargininal semicarbazone by mixed melting point with an authentic sample.[8] On evaporation of the third fraction followed by recrystallization from MeOH–AcOEt gave colorless crystals (0.8 g), mp 133—136°. This material was identical with the Cbz-N^G-nitroargininol prepared from Cbz-N^G-nitroarginine methyl ester by an alternative way described below.

Preparation of Cbz-Aminoalcohol from the Corresponding Aminoaldehydes to Compare the Optical Rotation with the Authentic Optically Pure Materials——The procedure described below were carried out in Cbz-N^G-

14) E. Schroeder, *Ann.*, **670**, 127 (1963).

nitroargininal, Cbz-leucinal, Cbz-phenylalaninal and Cbz-S-Bzl-cysteinal. The reduction with $(i\text{-}Bu)_2AlH$, which followed by TLC have been stopped before the desired Cbz-aminoaldehyde was further reduced to the corresponding aminoalcohol. The AcOEt extract of $(i\text{-}Bu)_2AlH$ reduction on Cbz-amino acid ester was evaporated *in vacuo* below 40°. The residue which contained Cbz-α-aminoaldehyde was divided into four portions and each portion was led to the corresponding Cbz-aminoalcohol in the various ways as described below. In (1), a portion of the residue was reduced directly with $NaBH_4$. However, in (2) and (3) the aminoaldehyde derivative purified by chromatography on silica gel was reduced with the same reducing agent. The time adsorbed on silica gel was different between (2) and (3). In (4), Cbz-α-aminoaldehyde in the residue was immediately converted to its semicarbazone, which was purified by chromatography on silica gel. Then the aldehyde regenerated from the semicarbazone with formalin and hydrochloric acid was reduced to the corresponding alcohol derivative with $NaBH_4$. These aminoalcohol derivatives obtained, which were characterized by TLC with an authentic sample, were dried *in vacuo* at room temperature to constant weight using a rotary pump. The specific rotation was compared with the authentic Cbz-aminoalcohol prepared by a different procedure.

1. Direct Reduction of the Crude Cbz-α-Aminoaldehyde: About 3 g of the crude Cbz-α-aminoaldehyde was dissolved in EtOH (30 ml). To this solution cooled in ice-water, 1 mM $NaBH_4$ solution (3 ml) in EtOH was added dropwise with stirring. After stirring for additional 20 min, AcOH (0.5 ml) was added to decompose excess $NaBH_4$ and the solvent was evaporated *in vacuo*. The residue was extracted with $CHCl_3$ and the $CHCl_3$ layer was washed with H_2O, dried over Na_2SO_4 and concentrated to give a syruppy residue (about 3 g). The syrup was applied on a column of silica gel (40 g) and the column was eluted with $CHCl_3$–MeOH (100:1, v/v) giving two fractions. The first fraction was the starting Cbz-amino acid ester (about 1.8—2.0 g). Under these reaction conditions, $NaBH_4$ reduced the aldehydes much faster than the esters. The second fraction afforded the Cbz-aminoalcohol (0.6—0.8 g), which was identified in comparison with the authentic sample (described below) by TLC. In the case of Cbz-N^G-nitroargininal, the extraction was carried out with AcOEt after $NaBH_4$ reduction. The reaction mixture applied on silica gel was eluted with $CHCl_3$–MeOH (100:4,v/v).

2. Reduction of Cbz-α-Aminoaldehyde after 6 hr Exposure to Silica gel: About 3 g of the crude Cbz-α-aminoaldehyde was applied on a column of silica gel (40 g). After standing for 6 hr at room temperature, the column was eluted with $CHCl_3$. The fractions were monitored by TLC. Cbz-amino acid ester, starting material, was eluted prior to Cbz-α-aminoaldehyde. The latter fraction was collected and evaporated *in vacuo* below 40°. To an ice-cooled solution of the purified aminoaldehyde derivative (0.6—0.8 g) in EtOH (10 ml), 1 mM $NaBH_4$ solution (3 ml) in EtOH was added with stirring. The reaction mixture was stirred for an additional 20 min and then AcOH (0.5 ml) was added to decompose excess $NaBH_4$. After the solvent was evaporated to dryness, the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4 and concentrated to give a syrup (about 0.5—0.7 g). The syrup was applied on a column of silica gel (10 g). Elution with $CHCl_3$–MeOH (100:1, v/v) and removal of the solvent gave the Cbz-aminoalcohol (about 0.4—0.6 g), which was identified in comparison with the authentic sample (described below) by TLC. In Cbz-N^G-nitroargininol, the extraction was carried out with AcOEt and purified by chromatography on silica gel eluted with $CHCl_3$–MeOH (100: 4, v/v).

3. Reduction of Cbz-α-Aminoaldehyde after 22 hr Exposure to Silica gel: The Cbz-aminoalcohol was obtained in the same way as described in 2, except that the exposure time of Cbz-α-aminoaldehyde to silica gel was extended to about 22 hr.

4. Reduction of Cbz-α-Aminoaldehyde Regenerated from Its Semicarbazone: As soon as the reduction with $(i\text{-}Bu)_2AlH$ was over, about 4 g of the crude Cbz-α-aminoaldehyde was dissolved in 70% EtOH (28 ml). After addition of semicarbazide hydrochloride (1.0 g) and sodium acetate (0.75 g), the mixture was allowed to stand for 5 min at 80°. The solvent was evaporated and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo*, giving a syrup (about 4 g). This syrup was purified by chromatography on silica gel (28 g) eluted with $CHCl_3$–MeOH (100:1, v/v), affording the Cbz-amino acid ester (1.8—2.0 g) as first fraction. Then the Cbz-α-aminoaldehyde semicarbazone (0.9—1.2 g) was obtained. To the solution of the semicarbazone (about 1 g) in EtOH (30 ml), 0.5N HCl (10 ml) and 37% formalin (3 ml) were added. The resulting solution was stirred at room temperature for 2 hr and diluted with H_2O (30 ml). The reaction mixture was extracted twice with AcOEt (70 ml). The organic layer was washed with H_2O, dried over Na_2SO_4 and then evaporated to dryness *in vacuo* below 40°. To an ice-cooled solution of the residue (about 0.9 g) in EtOH (20 ml), 1 mM $NaBH_4$ solution (5 ml) in EtOH was added dropwise under stirring. After stirring for additional 20 min, AcOH (0.6 ml) was added to decompose excess $NaBH_4$ and the solvent was evaporated *in vacuo*. The residue was dissolved in $CHCl_3$ (50 ml) and the solution was washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo* to a syruppy residue (0.6—0.8 g). The syrup applied on a silica gel column (15 g), was eluted with $CHCl_3$–MeOH (100:1, v/v) giving the Cbz-aminoalcohol (0.5—0.7 g), which was identified in comparison with the authentic sample (described below) by TLC. In Cbz-N^G-nitroargininal, the regenerated aldehyde from its semicarbazone was extracted with AcOEt. After $NaBH_4$ reduction of the argininal derivative, the corresponding aminoalcohol was extracted with AcOEt and purified by chromatography on silica gel eluted with $CHCl_3$–MeOH (100: 4, v/v).

General Procedure for the Synthesis of Authentic Optically Pure Cbz-Aminoalcohol——The physical data are given in Table IV. To an ice-cooled and stirred solution of Cbz-amino acid ester (6.5 mmoles) in EtOH (100 ml), 1 mM $NaBH_4$ solution (100 ml) in EtOH was added. The reaction mixture was stirred at room temperature for 3 hr. The excess $NaBH_4$ was decomposed by slow addition of 50% AcOH under cooling with ice water. After the reaction mixture was concentrated to about 70 ml *in vacuo* below 40° and diluted with H_2O (100 ml), extraction was carried out with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo* to dryness. The residue was purified by chromatography on silica gel (65 g) eluted with $CHCl_3$–MeOH (100:1, v/v). First the starting Cbz-amino acid ester and then the desired Cbz-aminoalcohol were eluted out. Recrystallization of the latter from ether-pet. ether gave crystalline powder. In the case of Cbz-N^G-nitroargininol, the aminoalcohol derivative was precipitated after $NaBH_4$ reduction and the filtered precipitate was purified by recrystallization from MeOH–AcOEt.