BIOORGANIC CHEMISTRY 18, 199–206 (1990)

Stereochemistry of the Michael Addition of Lysine Derivatives to α-Methylene-γ-butyrolactones

PATRICE TALAGA, CLAUDE BENEZRA, AND JEAN-LUC STAMPF

Laboratoire de Dermatochimie, Associé au CNRS, Université Louis Pasteur Clinique Dermatologique, CHU, 67091 Strasbourg, France

Received August 28, 1989

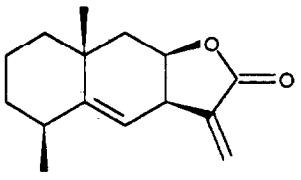
The stereochemistry of Michael additions of Boc-protected lysine derivatives (*N*-Boc-lysine-OMe and *N*-Boc-lysinyl-alanine-OMe) to natural sesquiterpene α-methylene-γ-butyrolactones has been investigated. © 1990 Academic Press, Inc.

A number of plants, especially *Compositae,* contain sesquiterpene lactones which are responsible for allergic contact dermatitis (ACD) (*1*). For example, alantolactone **1** and its structural isomer, isoalantolactone **2** (Fig. 1) are allergenic lactones (*2*) which are isolated from Helenin (Sigma), an extract of *Inula helenium* L.

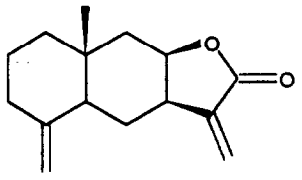
Their ability to induce ACD is related to their binding capacity to proteins containing nucleophilic groups such as -SH of cysteine and -ε-NH_2 of lysine (*3*) which react by the Michael addition to the electrophilic 1,4-unsaturated system of the γ-lactone. It is well known (*4–7*) that such compounds can react *in vitro* or *in vivo* with cysteine or polypeptides containing cysteine residues, the α-methylene-γ-butyrolactone acting as an alkylating agent. In literature, coupling of α-methylene-γ-butyrolactones with amines such as diethylamine (*8*), morpholine (*9*), and pentylamine (*9*), which react in a nearly quantitative yield, is reported. Reaction of an aminoethylpolystyrene with methylenelactones has also been reported (*10*). Apparently, coupling biological amines (such as lysine) to sesquiterpene lactones (*11*) under quasi-physiological conditions (pH 7.4) is a difficult reaction. To our knowledge, only one paper mentioned coupling between lysine and alantolactone **1** (*12*), but the analytical data of the adduct were not satisfactory.

In our search for skin tolerance inducers against the allergenic α-methylene-γ-butyrolactone moeity, we synthesized hydrosoluble lysine derivatives of **1** and **2.** Hydrosoluble derivatives of haptens, when given by a parenteral route, usually induce immunological tolerance to the related hapten (*13*). In this paper, we describe the synthesis of such adducts starting from fully protected lysine compounds: Boc-lysine(N^6-Z)-OMe **5** and Boc-lysinyl(N^6-Z)-alanine-OMe **6** (Scheme 1). In earlier experiments, when unprotected lysine was reacted with **1** or **2** at "physiological" pH (7.4) in a mixture of tetrahydrofuran (THF) and phosphate buffer 0.2 M, after 4 days of reaction, no coupling to the lactone was observed. Standard methods for liquid phase peptide synthesis were followed (Scheme 1) (*15, 17*).

0045-2068/90 $3.00



1 : ALANTOLACTONE



2: ISOALANTOLACTONE

FIG. 1

In order to determine whether or not racemization occurred during the peptide coupling procedure or during the selective deprotection of the Z group by catalytic transfer hydrogenation (see Scheme 1), we also prepared the Boc-protected (DL)-lysyl-(L)-alanine and (L)-lysyl-(DL)-alanine methyl esters (**6a** and **6b**) and compared their NMR spectra with those of the dipeptide obtained from pure L-amino acids. The results are collected in Table 1.

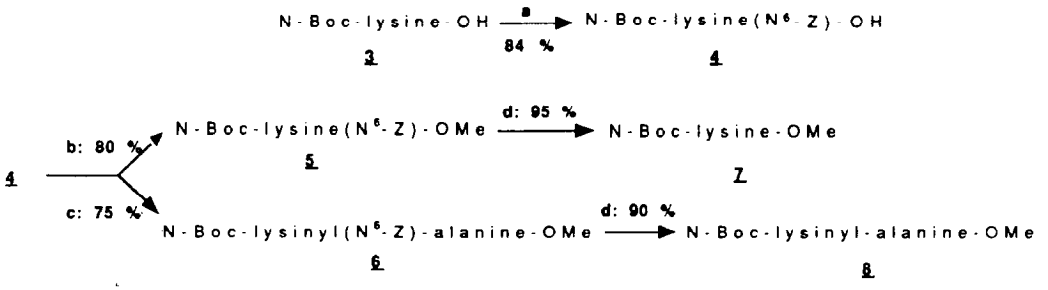
A comparison of the 200-MHz spectra of the Boc-L-lysinyl(N^6-Z)-L-alanine-OMe **6, 6a** and **6b** shows the following differences:

—only one -COOMe peak is observed in the spectrum of **6** while two -COOMe peaks appear in peptides obtained from racemic (DL)-lysine and (DL)-alanine-OMe (Table 1, **6a** and **6b**).

—only one CH_3-alanine doublet is present in the spectrum of **6** (and **6a**), although two doublets are seen for the diastereomeric peptide **6b.**

In the -ε-NH_2 deprotected peptide **8,** only the CH_3-alanine group is diagnostic of possible racemization. Moreover, the NMR spectra had to be obtained in C_6D_6 solutions, at 338°K to reveal the difference. In peptide **8,** the CH_3-alanine gives rise to a doublet. When racemization occurs at the C-α center of lysine, two CH_3 doublets are observed (Table 1, compound **9**).

In conclusion, the 200-MHz ^1H NMR spectra of the Boc-protected dipeptide



a. Z-Cl, NaOH, H_2O (ref 14) b: DCC, DMAP, CH_2Cl_2, MeOH (ref15) c: N-methylmorpholine, isobutyl chloroformate, THF, DMF, alanine-OMe (ref 16) d: 10% Pd/C, cyclohexadiene, EtOH (ref 17)

SCHEME 1

TABLE 1

Boc-Protected Dipeptide Methyl Esters

	Dipeptide	Anal.: Calcd/(found) C	H	N	^{1}H NMR date[a] of -OMe	-CH_3-Ala
6	Boc-L-Lys(N^6-Z)-L-Ala-OMe	59.34 (59.52)	7.5 (7.45)	9.02 (8.95)	3.71 s	1.40 d J_{H-H} = 7.3
6a	Boc-(DL)-Lys(N^6-Z)-L-Ala-OMe[b]	59.34 (59.10)	7.57 (7.56)	9.02 (8.87)	3.73 and 3.72 2s	1.43 d J_{H-H} = 7.3
6b	Boc-L-Lys(N^6-Z)-(DL)-Ala-OMe[c]	59.34 (59.59)	7.57 (7.69)	9.02 (8.84)	3.72 and 3.69 2s	1.39 2d
8	Boc-L-Lys-L-Ala-OMe		nd[d]		3.38 s	1.31 d J_{H-H} = 7.2
9	Boc-(DL)-Lys-L-Ala-OMe		nd[d]		3.37 s	1.30 2d J_{H-H} = 7.2
10	Boc-L-Lys-(DL)-Ala-OMe		nd[d,e]			

[a] For compounds **6** to **6b**, ^{1}H NMR spectra were recorded in $CDCl_3$ at 35°C. For compounds **8** to **10**, ^{1}H NMR spectra were recorded in C_6D_6 at 65°C. Chemical shifts are reported in δ ppm with respect to TMS as internal standard. Coupling constants (J) are expressed in hertz. Multiplicities are indicated by s (singlet), d (doublet), and 2d (two doublets). Note that for compound **9** only the -CH_3-alanine-OMe moiety shows extra signals evidencing that racemization had occurred.

[b] Prepared from Boc-(DL)-lysine(N^6-Z)-OH (*18*) and L-alanine-OMe according to the "mixed carbon anhydride" method (*16*).

[c] (DL)-Alanine-OMe was purchased from Sigma and was used without further purification.

[d] nd, not done since the *unstable* ε-NH_2-deprotected dipeptide was always immediately coupled to α-methylene-γ-butyrolactone.

[e] Deprotection was incomplete, under conditions identical to those used for the deprotection of compounds **8** and **9**.

methyl esters show that no significant racemization has occurred during peptide synthesis and during Z deprotection of the ε-NH_2 function of lysine.

Coupling Procedure

Coupling of *N*-Boc-lysine-OMe **7** and *N*-Boc-lysinyl-alanine-OMe **8** to alantolactone **1** and isoalantolactone **2** was performed in benzene at room temperature for 24 h (see below, typical procedure). When the reaction was done in other solvents such as methanol or acetonitrile, yields of adducts decreased dramatically (<40% in all cases) and many by-products were formed.

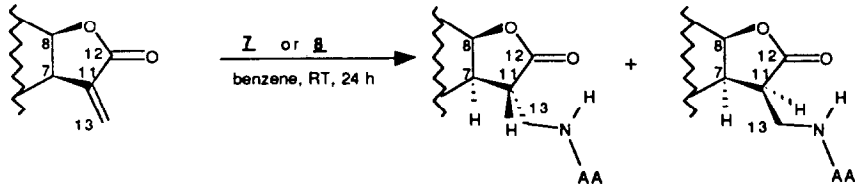
Results of the Michael addition of **7** and **8** to lactones **1** and **2** are collected in Table 2.

Some observations can be made:

—When *N*-Boc-lysine-OMe **7** was coupled to lactone **1** or **2** the selectivity of the addition was not total (see Table 2, adducts **11** and **12**, (Fig. 2). The yield of the reaction was about 60%, indicating that the ε-NH_2 group is not a powerful nucleophile under these conditions.

TABLE 2

Michael Addition Reaction of Lysine Derivatives **7** and **8** to Lactones **1** and **2**



1 or **2** H_7-H_{11} anti Adduct H_7-H_{11} syn Adduct

Lysine derivative	Lactone[a]	Adduct[b]	Yield[c]	Anal.: Calcd/(found) C	H	N	*anti*[d] : *syn*[d]
7	**1**	**11**	64	65.82	9.00	5.68	1 : 2
				(65.73)	(9.18)	(5.81)	($J_{H7\text{-}H11}$ = 0) ($J_{H7\text{-}H11}$ = 7.3)
7	**2**	**12**	60	65.82	9.00	5.68	nd[e] : nd[e]
				(65.95)	(8.91)	(5.71)	
8	**1**	**13**	40	63.92	8.76	7.45	Not detected : >95%
				(63.64)	(8.75)	(7.18)	($J_{H7\text{-}H11}$ = 7.3)
8	**2**	**14**	40	63.92	8.76	7.45	>95% : Not detected
				(63.98)	(8.66)	(7.18)	($J_{H7\text{-}H11}$ = 0)

[a] Alantolactone **(1)** and isoalantolactone **(2)** were obtained as reported (*2*) from Helenin a commercial extract of *Inula helenium* L. (Sigma).

[b] See Figs. 2 and 3. All adducts were oils.

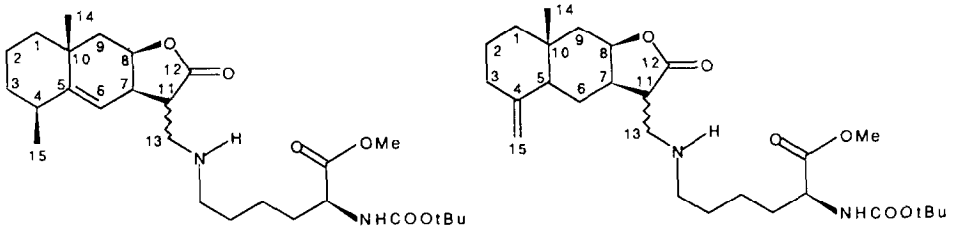
[c] After purification by chromatography on silica gel.

[d] ^{1}H NMR data are in full agreement with the structural assignments. Stereochemistry of the C_7 and C_{11} center is based on 400 MHz ^{1}H NMR (compounds **11, 14**) and COSY 400 MHz ^{1}H NMR (compound **1**) study.

[e] nd, not determined: no configuration assignment could be made with certainty by ^{1}H NMR spectroscopy.

—When *N*-Boc-lysinyl-alanine-OMe **8** was coupled to **1** or **2,** the yield of the reaction decreased to 40%, perhaps because of steric hindrance.

—The reaction is, however, highly stereoselective (see Table 2, adducts **13** and **14,** Fig. 3) and depends on the nature of the lactone. NMR COSY experiments at 400 MHz allowed us to determine the *syn* or the *anti* nature of the H_7-H_{11} arrangement. COSY was only used to determine the spin–spin coupling. H_7 was irradiated and H_{11} observed and conversely. Thus, if the dipeptide **8** was coupled to alantolactone **1,** the major product **13** had a H_7-H_{11} *syn* configuration, as shown by a 7.3-Hz coupling constant. This can only correspond to a 90° dihedral angle (Karplus relationship of the vicinal coupling dependence on dihedral angle). However, when **8** was coupled to isoalantolactone **2** the major product **14** had a H_7-H_{11} *anti* configuration, as evidenced by a 0-Hz coupling constant. Dreiding models with both H_7-H_{11} *syn* and H_7-H_{11} *anti* configurations clearly showed geometries corresponding respectively to 90° and 30°.



11 12

FIG. 2

For comparison, Boc-protected cysteine dipeptide methyl esters (Boc-Cys-Ala-OMe), when reacted with *cis*-fused α-methylene-γ-butyrolactones such as **1, 2,** and others at physiological pH, gave exclusively H_7-H_{11} *anti* adducts (*19*). These products **(11–14)** gave, after Boc cleavage under mild acid conditions (trifluoroacetic acid-methylene chloride (CH_2Cl_2), 1/1), hydrosoluble lactone derivatives which will be tested for their biological activity as skin tolerance inducers in the guinea pig.

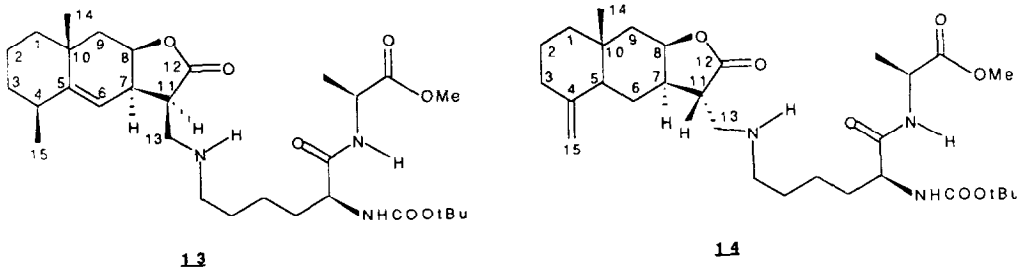
The biological study is still in progress and will be published in due course.

EXPERIMENTAL SECTION

General Methods

Proton NMR spectra of samples were recorded on 60-, 200-, and 400-MHz Brucker spectrometers in $CDCl_3$ or C_6D_6. Chemical shifts are indicated in δ ppm with respect to TMS as internal standard (δ = 0). Infrared spectra were obtained on a Beckman Acculab spectrometer using $CHCl_3$ solutions.

Dry solvents were freshly distilled before use. THF was distilled from sodium benzophenone. Dimethylformamide (DMF) was stored over 4-Å molecular sieves. CH_2Cl_2 was distilled from P_2O_5. Chromatographic purifications were conducted at normal pressure on silica gel columns.



13 14

FIG. 3

N-Boc-L-lysine(N^6-Z)-OH **4** was prepared from commercially available *N*-Boc-L-lysine (Fluka), protected at the ε-NH_2 end with benzyl chloroformate according to Ref. (*14*).

Lysine Derivatives

N-Boc-L-lysine(N^6-Z)-OMe **(5).** To a stirred solution of *N*-Boc-L-lysine(N^6-Z)-OH **4** (1 g, 2.62 mmol) in dry CH_2Cl_2 (20 ml) at room temperature was added, respectively, 1.1 eq (594.7 mg, 2.88 mmol) of dicyclohexylcarbodiimide, 1.1 eq (0.12 ml) of anhydrous methanol, followed by 0.1 eq (32 mg) of dimethylaminopyridine. After 1.5 h of stirring at room temperature, the reaction mixture was filtered off (to remove dicyclohexylurea) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluant: CH_2Cl_2/AcOEt, 5/1).

Compound **5** (829 mg, 2.1 mmol) was obtained as an colorless oil. Yield: 80%. ir (cm^{-1}): 3430, 2925, 1740, 1670. NMR (200 MHz): 7.33 (5H, s, phenyl); 5.09 (3H, broad s, NH, phenyl-CH_2); 4.27 (1H, m, Hα-Lys); 3.73 (3H, s, OMe); 3.17 (2H, dt, $J_{H\text{-}NH} = J_{H\text{-}H} = 6.30$, ε-CH_2-Lys); 1.43 (9H, s, t-Bu); 1-2 (6H). $[a]^{20}D = +7.8$ (c: 3.93 g/100 ml in $CHCl_3$). *Anal.* Calcd for $C_{20}H_{30}N_2O_6$: C, 60.90; H, 7.66; N, 7.10. Found: C, 61.11; H, 7.85; N, 7.22.

N-Boc-L-lysine(N^6-Z)-L-alanine-OMe **(6).** A solution of *N*-Boc-L-lysine(N^6-Z)-OH (2.17 g, 5.7 mmol) in dry THF (20 ml) under argon was cooled to -15°C (CCl_4, dry ice) with stirring; 1.1 eq (0.68 ml) of *N*-methylmorpholine was added, followed by 1.2 eq (0.89 ml) of isobutyl chloroformate. Five minutes later, a solution of alanine methyl ester (1.1 eq, 875.2 mg) in DMF was added. After 5 min, the CCl_4 dry ice bath was removed and the solution allowed to stand for 20 h at room temperature. After concentration under vacuum, the residue was taken up in ethyl acetate and water. After extraction, the aqueous phase was discarded and the organic phase was washed successively with 10 ml of a saturated sodium bicarbonate solution, 10 ml of water, 10 ml of 1 N hydrochloric acid, and 10 ml of water. The solution was dried over dry magnesium sulfate, filtered, and concentrated under vacuum. The peptide was purified by silica gel column chromatography using CH_2Cl_2/AcOEt, 5/2, as eluant. Compound **6** (1.99 g, 4.27 mmol) was obtained as an oil. Yield: 75%, See Table 1.

N-Boc-(DL)-lysine(N^6-Z)-L-alanine-OMe **(6a).** The reaction was performed as above. From 500 mg (1.31 mmol) of *N*-Boc-(DL)lysine(N^6-Z)-OH was obtained 363.2 mg (0.78 mmol) of **6a.** Yield: 60%. See Table 1.

N-Boc-L-lysine(N^6-Z)-(DL)-alanine-OMe **(6b).** The reaction was performed as above. From 500 mg (1.31 mmol) of *N*-boc-L-lysine(N^6-Z)-OH was obtained 396 mg (0.85 mmol) of **6b.** Yield: 65%. See Table 1.

N-Boc-L-lysine-OMe **(7).** To a solution of *N*-Boc-L-lysine(N^6-L-lysine(N^6-Z)-OMe **5** (725.9 mg, 1.84 mmol) in absolute ethanol (8 ml) under argon at 35°C was added 1 eq (726.5 mg) of 10% Pd/C, followed by 10 eq (1.74 ml) of cyclohexadiene. The deprotection was quantitative after a 1-h reaction time. The reaction mixture was filtered through a Celite 545 pad. The filtrate was then evaporated under reduced pressure and compound **7** (430 mg, 1.65 mol) was obtained in a suffi-

ciently pure form to be directly used without purification in the following step. Yield: 95%. ir (cm^{-1}): 3440, 3300, 2910, 1740, 1660. NMR (60 MHz): 5.32 (1H, m, NH); 4.19 (1H, m, Hα-Lys); 3.68 (3H, s, OMe); 2.66 (2H, m, ε-CH_2-Lys); 1.43 (9H, s, t-Bu); 1-2 (6H,-$CH_2CH_2CH_2$- of lysine).

N-Boc-L-lysinyl-L-alanine-OMe **(8).** The reaction was performed as above. From 500 mg (1.07 mmol) of *N*-Boc-L-lysinyl(N^6-Z)-L-alanine-OMe was obtained 318.2 mg (0.96 mmol) of **8.** Yield: 90%. See Table 1.

N-Boc-(DL)-lysinyl-L-alanine-OMe **(9).** The reaction was performed as above. From 500 mg (1.07 mmol) of *N*-Boc-(DL)-lysinyl(N^6-Z)-L-alanine-OMe was obtained 318.2 mg (0.96 mmol) of **9.** Yield: 90%. See Table 1.

Typical Procedure: Lactone–Lysine Derivatives Coupling

The lysine derivative (1 mmol) was dissolved in anhydrous benzene (5 ml) under argon. The α-methylene-γ-butyrolactone (1 mmol) was added in one portion and the reaction mixture left at room temperature for 24 h. It was then evaporated under reduced pressure and the crude product purified by silica gel column chromatography using CH_2Cl_2/MeOH (9/0.5) as eluent. All adducts were oils and gave satisfactory analytical and spectral data. See Table 2. Thus compounds **11–14** were obtained.

N-Boc-L-lysine(N^6-alantolactone)-OMe **(11).** ir (cm^{-1}): 3300, 1770, 1745, 1680. NMR (400 MHz): 5.11 (1H, d, $J_{H\text{-}H}$ = 3.09, H_6); 5.09 (1H, d, $J_{H\text{-}H}$ = 7.5, α-NH); 4.79–4.77 (1H, m, H_8); 4.29 (1H, dt, $J_{H\text{-}H}$ = $J_{H\text{-}NH}$ = 7.50, α-H); 3.79 (1/3 of 3H, s, OMe); 3.74 (2/3 of 3H, s, OMe); 3.18–3.14 (1H, m, H_7); 3.10 (1H, dt, $J_{H11\text{-}H7}$ = 7.30, H_{11}); 2.93–2.91 (2H, m, $CH_{2(13)}$); 2.71 (2H, t, $J_{H\text{-}H}$ = 7.30, ε-CH_2-Lys); 2.48 (1H, m, H_4); 2.10 (1H, dd $J_{H\text{-}H}$ = 3.26, 1H of $CH_{2(9)}$); 1.82–1.80 (2H, m, CH_2α-Lys); 1.46 (1/3 of 9H, s t-Bu); 1.45 (2/3 of 9H, s, t-Bu); 1.23 (3H, s, $CH_{3(14)}$); 1.12 (3H, d, $J_{H\text{-}H}$ = 7.60, $CH_{3(15)}$). *Anal.* See Table 2.

N-Boc-lysine(N^6-isoalantolactone)-OMe **(12).** ir (cm^{-1}): 3300, 1765, 1740, 1690. NMR (200 MHz): 5.05 (1H, d, $J_{H\text{-}H}$ = 7.5, α-NH); 4.77 (1H, s, H_{15}); 4.49 (1H, m, H_8); 4.45 (1H, s, H_{15}); 4.27 (1H, m, α-H); 3.73 (3H, s, OMe); 3.06–2.88 (2H, m, $CH_{2(13)}$); 2.88–2.82 (2H, m, ε-CH_2-Lys); 2.80–2.73 (1H, m, H_{11}); 2.54–2.46 (1H, m, H_7); 2.20–2.19 (1H, m, 1H of $CH_{2(9)}$); 1.43 (9H, s, t-Bu); 0.80 (3H, s, $CH_{3(14)}$). *Anal.* See Table 2.

N-Boc-L-lysinyl(N^6-alantolactone)-L-alanine-OMe **(13).** ir (cm^{-1}): 3300, 1763, 1730, 1710, 1685. NMR (COSY 400 MHz): 6.76 (1H, d, $J_{H\text{-}H}$ = 7.23, NH-Ala); 5.15 (1H, m, α-NH-Lys); 5.14 (1H, d, $J_{H\text{-}H}$ = 3.05, H_6); 4.76–4.75 (1H, m, H_8); 4.57 (1H, dq, $J_{H\text{-}H}$ = $J_{H\text{-}NH}$ = 7.30; α-H-Ala); 4.08 (1H, m, Hα-Lys); 3.74 (3H, s, OMe); 3.16–3.12 (1H, m, H_7); 3.03 (1H, dt, $J_{H7\text{-}H11}$ = 7.30, H_{11}); 2.87 (2H, AB part of an ABX, J_{AX} = 3.43; J_{BX} = 3.84; δ_A = 2.82; δ_B = 2.93, J_{AB} = 14; $CH_{2(13)}$); 2.71–2.66 (2H, m, ε-CH_2-Lys); 2.48 (1H, m, H_4); 2.10 (1H, dd, $J_{H\text{-}H}$ = 3.25 Hz, 1H of $CH_{2(9)}$); 1.44 (9H, s, t-Bu); 1.40 (3H, d, $J_{H\text{-}H}$ = 7.20; CH_3-Ala); 1.23 (3H, s, $CH_{3(14)}$); 1.12 (3H, d, $J_{H\text{-}H}$ = 7.57; $CH_{3(15)}$). $[a]^{20}D$: −16 (c: 0.69 g/100 ml in CCl_4). *Anal.* See Table 2.

N-Boc-L-lysinyl(N^6-isoalantolactone)-alanine-OMe **(14).** ir (cm^{-1}): 3300, 1765, 1740, 1715, 1687. NMR (400 MHz): 6.82 (1H, d, $J_{H\text{-}H}$ = 7.0, NH-Ala); 5.12 (1H, m,

α-NH-Lys); 4.79 (1H, s, H_{15}); 4.69 (1H, dq, $J_{H\text{-}H} = J_{H\text{-}NH} = 7.30$, H$\alpha$-Ala); 4.52 (1H, m, H_8); 4.47 (1H, s, H_{15}); 4.10 (1H, m, Hα-Lys); 3.74 (3H, s, OMe); 3.09–3.05 (2H, m, $CH_{2(13)}$); 2.91–2.88 (1H, m, H_{11}); 2.75 (2H, t, $J_{H\text{-}H} = 6.97$, ε-CH_2-Lys); 2.58–2.55 (1H, m, $J_{H7\text{-}H11} = 0$, H_7); 2.20–2.15 (1H, m, 1H of $CH_{2(9)}$); 1.45 (9H, s, t-Bu); 1.42 (3H, d, $J_{H\text{-}H} = 7.30$, CH_3-Ala); 1.23–1.21 (2H, m, $CH_{2(6)}$); 0.81 (3H, s, $CH_{3(14)}$). [a] $^{20}D = +16$ (c: 0.92 g/100 ml in $CHCl_3$). *Anal.* See Table 2.

ACKNOWLEDGMENT

A most careful reading of the manuscript by one of the Referees is gratefully acknowledged.

REFERENCES

1. MITCHELL, J. C., AND DUPUIS, G. (1971) *Brit. J. Dermatol.* **84,** 139–150.
2. STAMPF, J. L., BENEZRA, C., KLECAK, G., GELEIK, H., SCHULTZ, K. H., AND HAUSEN, B. M. (1982) *Contact Dermatitis* **8,** 16–24.
3. MACHER, E., AND CHASE, M. W. (1969) *J. Exp. Med.* **129,** 103–151.
4. KUPCHAN, S. M., EAKIN, M. A., AND THOMAS, A. M. (1971) *J. Med. Chem.* **14,** 1147–1152.
5. RODRIGUEZ, E., TOWERS, G. H. N., AND MITCHELL, J. C. (1976) *Phytochemistry* **15,** 1573–1580.
6. HALL, I. H., LEE, K. H., MAR, E. C., AND STARNES, C. O. (1977) *J. Med. Chem.* **20,** 333–336.
7. CASSADY, J. M., BYRN, S. R., STAMOS, I. K., EVANS, S. M., AND MCKENZIE, A. (1978) *J. Med. Chem.* **21,** 815–819.
8. CHEMINAT, A., BENEZRA, C., AND FRÉCHET, J. M. J. (1982) *J. Chem. Res. Synop.,* 148; (1982) *J. Chem. Res. Miniprint,* 1618–1632.
9. KAWAMATA, T., AND INAYAMA, S. (1971) *Chem. Pharm. Bull.* **19,** 643–644.
10. CHEMINAT, A., BENEZRA, C., FARRALL, M. J., AND FRÉCHET, J. M. J. (1981) *Canad. J. Chem.* **59,** 1405–1414.
11. KUPCHAN, S. M., FESSLER, D. C., EAKIN, M. A., AND GIACOBBE, T. J. (1970) *Science* **168,** 376–377.
12. DUPUIS, G., MITCHELL, J. C., AND TOWERS, G. H. N. (1974) *Canad. J. Biochem.* **52,** 575–581.
13. CLAMAN, H. N., MILLER, S. D., SY, M. S., AND MOORHEAD, J. W. (1980) *Immunol. Rev.* **50,** 105–132.
14. WUNSCH, E. (1986) *Synthesis,* 958–960.
15. HASSNER, A., AND ALEXANIAN, V. (1978) *Tetrahedron Lett.,* 4475–4478.
16. ANDERSON, G. W., ZIMMERMAN, J. E., AND CALLAHAN, F. M. (1967) *J. Amer. Chem. Soc.* **89,** 5012–5017.
17. FELIX, A. M., HEIMER, E. P., LAMBROS, T. J., TZOUGRAKI, C., AND MEIENHOFER, J. (1978) *J. Org. Chem.* **43,** 4194–4196.
18. Boc-(DL)-lysine(N^6-Z)-OH was prepared from (DL)-lysine which was protected selectively at the ε-NH_2 group with Z-OSu (benzyl succinimidyl carbonate), according to Paquet's procedure (PAQUET, A. (1976) *Canad. J. Chem.* **54,** 733–737) and then protected at the α-NH_2 end with Boc-ON (2-*tert*-butyloxycarbonyloxyimino-2-phenylacetonitrile) according to Itoh's *et al.* procedure ((1975) *Tetrahedron Lett.,* 4393–4394).
19. TALAGA, P., SCHAEFFER, M., BENEZRA, C., AND STAMPF J. L. (1989) *Tetrahedron* **45,** 5029–5038.