A Practical Synthesis of an Orally Potent Renin Inhibitor, Isopropyl (2*R*,3*S*)-4-Cyclohexyl-2-hydroxy-3-{*N*-[(2*R*)-2-morpholinocarbonylmethyl-3-(1-naphthyl)propionyl]-L-histidyl}aminobutyrate

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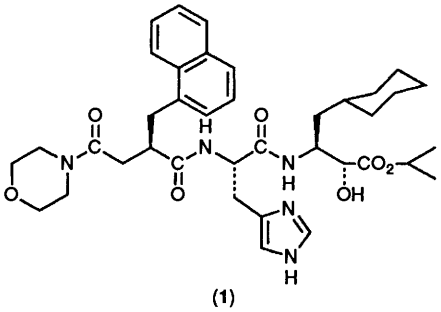
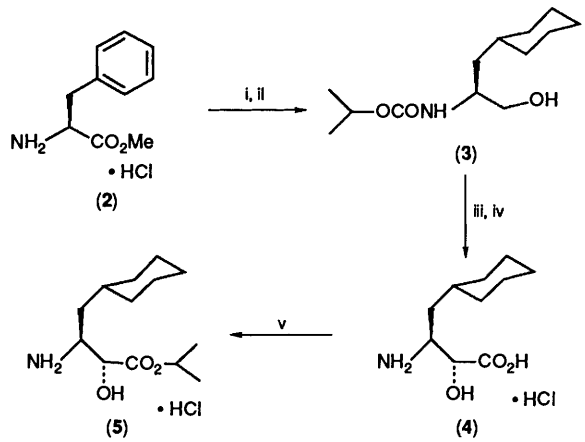
The practical synthesis of an orally potent human renin inhibitor, isopropyl (2*R*,3*S*)-4-cyclohexyl-2-hydroxy-3-{*N*-[(2*R*)-2-morpholinocarbonylmethyl-3-(1-naphthyl)propionyl]-L-histidyl}-aminobutyrate, is presented. Optically pure cyclohexylnorstatine isopropyl ester (P_1–P_1' moiety) was diastereoselectively and simply prepared from L-phenylalanine methyl ester. In a *one-pot* reaction, *N*-[(2*R*)-2-morpholinocarbonylmethyl-3-(1-naphthyl)propionyl]-L-histidine methyl ester (P_4–P_2 moiety) was conveniently hydrolysed, protected with a Boc group attached to the side-chain imidazole function, and coupled with the cyclohexylnorstatine ester to give the optically pure target renin inhibitor.

Renin (EC 3.4.23.15) is an aspartic acid protease that selectively cleaves angiotensinogen to form the decapeptide, angiotensin I (Ang I). Ang I is then cleaved by angiotensin-converting enzyme, which is a non-specific dipeptidyl carboxypeptidase, to yield the biologically active octapeptide, angiotensin II (Ang II). Ang II acts as a potent pressor agent directly by virtue of its vasoconstricting activity. Renin catalyses the rate-limiting step in the renin–angiotensin system, and the action of renin on angiotensinogen is highly specific. Thus, a large number of renin inhibitors have been investigated as possible antihypertensive drugs.[1]



(1)

We have recently reported[2,3] a novel and low molecular weight renin inhibitor, isopropyl (2*R*,3*S*)-4-cyclohexyl-2-hydroxy-3-{*N*-[(2*R*)-2-morpholinocarbonylmethyl-3-(1-naphthyl)propionyl]-L-histidyl}aminobutyrate (**1**), which contains a (2*R*)-2-morpholinocarbonylmethyl-3-(1-naphthyl)-propionyl residue having *retro-inverso* amide bond,[4] L-histidine, and a novel amino acid, (2*R*,3*S*)-3-amino-4-cyclohexyl-2-hydroxybutyric acid, cyclohexylnorstatine (**4**),[5] as a transition-state mimic. Compound (**1**) was designed from the angiotensinogen transition-state based on a three-dimensional structure of the complex of human renin and the scissile site Pro-to-Val (P_4 to P_1')† of angiotensinogen deduced using modelling techniques.[6] The deduced active conformation of compound (**1**) was shown to fit the active site of renin favourably,[2,7] and the stereochemistry of compound (**1**) was important in its renin-inhibitory potency. Compound (**1**) is one of the lowest molecular weight compounds to exhibit highly selective renin-inhibitory activity *in vitro* and long-lasting hypotensive activity after oral administration.[8] Thus, optically pure compound (**1**) is required in large amounts for further evaluation as an antihypertensive drug candidate. In this paper, we describe a convenient and practical method for the synthesis of compound (**1**).



(2) (3) (4) (5)

Scheme 1. *Reagents and conditions:* i, isopropyl chloroformate. Et_3N, 0 °C, 1 h; ii, $NaBH_4$, LiCl, room temp., overnight; then H_2 (3–4 atm), Rh/Al_2O_3, 11 h; iii, $Py{\cdot}SO_3$–DMSO, 25 °C, 20 min; iv, NaCN–HCl, 0 °C, 3 h; then 23% HCl, 80 °C, 11 h; v, isopropyl alcoholic HCl, 80 °C, 1 h.

Cyclohexylnorstatine isopropyl ester (**5**) (P_1-P_1' moiety) was diastereoselectively and simply prepared by using the isopropoxycarbonyl group as an amine-protecting group as shown in Scheme 1. Isopropoxycarbonyl-L-phenylalanine methyl ester was prepared from L-phenylalanine methyl ester (**2**) by treatment with isopropyl chloroformate. On the other hand, use of t-butoxycarbonyl (Boc) reagents such as Boc-SDP,[9] Boc-ON,[10] and di-t-butyl dicarbonate (Boc_2O)[11] was rather troublesome due to the incomplete removal of unchanged Boc reagents or their fragments after the usual work-up.

† The positions (P) and subsites (S) are indicated according to the scheme of Schechter and Berger. (I. Schechter and A. Berger, *Biochem. Biophys. Res. Commun.*, 1967, **27**, 157).

Reduction of the methyl ester with $NaBH_4$–LiCl in tetrahydrofuran (THF)–ethanol at ambient temperature followed by hydrogenation with Rh/Al_2O_3 at 3–4 atm gave the cyclohexylalaninol (**3**) [86% yield from (**2**)]. Compound (**3**) was oxidized with $Py{\cdot}SO_3$–dimethyl sulphoxide (DMSO) in benzene at 25 °C,[12] and the product was hydrocyanated with NaCN–HCl in aq. $CHCl_3$ at 0 °C, followed by hydrolysis with 23% HCl at 80 °C for 11 h to provide the cyclohexylnorstatine as a 4:1 (2*R*:2*S*) diastereoisomeric mixture. The diastereoisomeric ratio was calculated from the ^1H NMR spectrum.[5] When the reaction mixture was kept overnight, optically pure cyclohexylnorstatine (**4**) exclusively crystallized out of the mixture in the form of the HCl salt [60% yield from (**3**)]. The diastereoisomeric ratio of cyclohexylnorstatine was greatly influenced by the nature of the amino-protecting group; *e.g.*, formyl group (2*R*:2*S* 1:1) and phthaloyl group (2*R*:2*S* 3:7) and by the solvent used in the hydrocyanation; *e.g.*, MeOH (2*R*:2*S* 1:1), aq. dimethylformamide (DMF) (2*R*:2*S* 1:1), aq. benzene (2*R*:2*S* 13:5), and aq. EtOAc (2*R*:2*S* 7:3). Thus, we conveniently prepared optically pure (**4**), which was esterified with isopropyl alcoholic HCl and the ester was recrystallized from ethyl acetate to give compound (**5**) (95% yield). The stereochemistry of compound (**5**) was determined by ^1H NMR spectroscopy.[2,5,7]

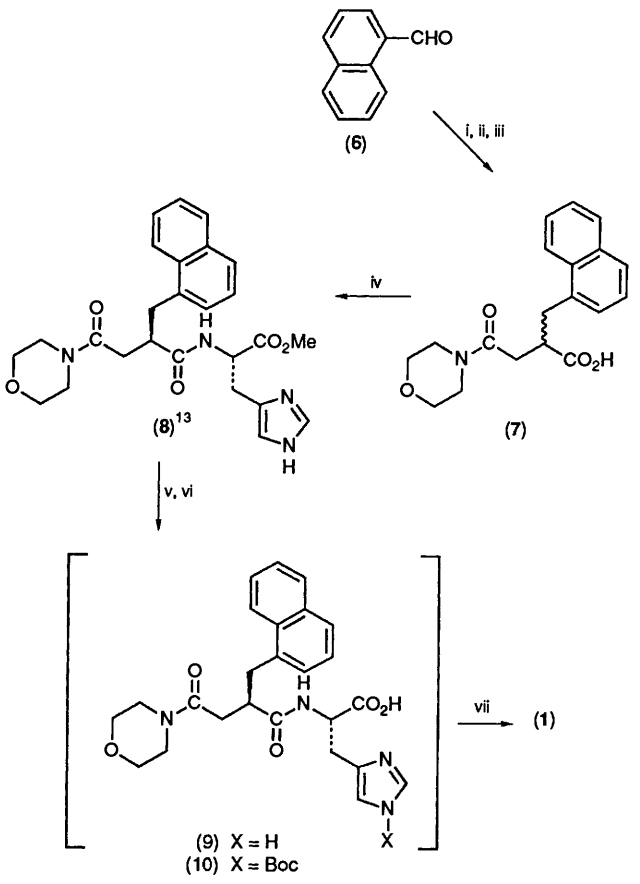
The propionic acid (**7**)[13] (P_4-P_3 moiety) was prepared from 1-naphthaldehyde (**6**) in high yield. Since attempted optical resolution of compound (**7**) with several optically active amines was unsuccessful, we investigated our recently found, efficient method for the synthesis of (2*R*)-2-morpholinocarbonylmethyl-3-(1-naphthyl)propionyl-L-histidine methyl ester (**8**)[13] (P_4-P_2 moiety) without the troublesome procedure of using optically active reagents and column chromatographic purification.[13] Compound (**8**) was hydrolysed and the product coupled with ester (**5**). However, the coupling yield (65%) was low due to the formation of by-products and the insolubility* of the product (**9**) and the purification of compound (**1**) was troublesome using column chromatography.

Therefore, we investigated a more convenient method for synthesis of target molecule (**1**) as shown in Scheme 2. After hydrolysis of the methyl ester (**8**) with aqueous NaOH, the imidazole function of the histidine moiety was protected with Boc_2O. *N*-[(2*R*)-2-Morpholinocarbonylmethyl-3-(1-naphthyl)-propionyl]-N^{im}-Boc-L-histidine (**10**) thus obtained exhibited high solubility. Without isolation of the product (for the sake of practicality)† compound (**10**) was coupled with the ester (**5**) using dicyclohexylcarbodi-imide (DCC) and *N*-hydroxy-norborn-5-ene-2,3-dicarboximide (HONB) in acetonitrile. After removal of the solvents, the residue was dissolved in ethyl acetate and the solution was washed successively with aqueous citric acid and aqueous $NaHCO_3$. Equimolar toluene-*p*-sulphonic acid (PTSA) was added to this solution, and then optically pure (**1**) exclusively crystallized out of the solution in the form of the toluene-*p*-sulphonate salt with concomitant deprotection of the Boc group attached to the imidazole function (80% overall yield). The optical purity of compound (**1**) was determined by HPLC analysis. Other protecting groups such as benzyloxycarbonyl, isopropoxycarbonyl, and toluene-*p*-sulphonyl groups did not give sufficient yield due to the unsuitable stability of the protecting groups.

Thus, optically pure (**1**), an orally potent human renin inhibitor, was synthesized conveniently without the use of complicated procedures such as the use of optically active reagents and column chromatography.

* Compound (**9**) was practically insoluble in almost all the common solvents except a mixture of DMF and DMSO.

† The isolation procedure and the physical and spectral characteristics of compound (**10**) are described in the Experimental section.



Scheme 2. *Reagents and conditions:* i, diethyl succinate, NaOMe, MeOH, reflux, 2 h; then aq. NaOH, reflux, 6 h; ii, $SOCl_2$, CH_2CH_2, reflux, 2 h; then morpholine, EtOAc, room temp. overnight; iii, H_2; Pd/C, MeOH, room temp., overnight; iv, His-OMe·HCl/DCC, HONB, acetonitrile, 0 °C–room temp., overnight; then recrystallization as salicylic acid salt from EtOAc; v, NaOH, MeOH, room temp., overnight; then HCl; vi, Boc_2O, Et_3N, 0 °C–room temp., overnight; vii, (**5**), DCC, HONB, acetonitrile, 0 °C–room temp., overnight; then PTSA, EtOAc, room temp.–40 °C.

Experimental

^1H NMR spectra were measured on a JEOL JMX-GX270 (270 MHz) instrument. Chemical shifts are reported as δ-values relative to Me_4Si or $Me_3Si[CH_2]_3SO_3Na$ as internal standard. Fast-atom bombardment (FAB-MS) spectra were obtained with a JEOL JMX-DX300 spectrometer coupled with a JMA-DA5000 data processor. IR spectra were measured on JASCO IR-810 infrared spectrophotometer. HPLC analyses were performed on a Shimadzu LC-6A liquid chromatograph instrument, YMC-Packed Column R-ODS-5, and 0.05M-aq. NH_4OAc–MeCN eluant, with UV detection at 223 nm (JASCO UVIDEC-100-V). Optical rotations were measured with a Horiba SEPA-200 high-sensitivity polarimeter. M.p.s were measured on a Yamato micro melting point apparatus and are uncorrected. Elemental analyses were performed by the Analytical Research Department, Central Research Laboratories, Kissei Pharmaceutical Co., Ltd.

N-(*Isopropoxycarbonyl*)-L-*cyclohexylalaninol* (**3**).—To a suspension of L-phenylalanine methyl ester hydrochloride (**2**) (20.0 g, 93 mmol) in THF (200 ml) at 0 °C were added triethylamine (25.8 ml, 186 mmol) and isopropyl chloroformate (12.5 ml, 93 mmol) simultaneously during 30 min. After 1 h at 0 °C, the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate, and the solution was washed

successively with 1M-HCl, 5% aq. $NaHCO_3$, and brine, and dried over $MgSO_4$. The solution was evaporated to give *N*-(isopropoxycarbonyl)-L-phenylalanine methyl ester (24.0 g, 97%).

To a solution of the methyl ester (6.2 g, 23 mmol) in THF (30 ml) were added anhydrous lithium chloride (3.0 g, 69 mmol), sodium borohydride (2.6 g, 69 mmol), and ethanol (60 ml). After the mixture had been stirred at room temperature overnight, aq. citric acid was added and the mixture was extracted with CH_2Cl_2. The extracts were washed successively with 5% aq. $NaHCO_3$ and brine, and dried over $MgSO_4$. Removal of the solvent gave *N*-(isopropoxycarbonyl)-L-phenylalaninol (5.2 g, 94.5%).

A solution of the alcohol (1.0 g, 4.2 mmol) in methanol (1.5 ml) was hydrogenated for 11 h in a Parr apparatus with 5% Rh/Al_2O_3 (50 mg). The hydrogen pressure was periodically adjusted to maintain 3–4 atm. The solution was filtered through Celite and evaporated to give *N*-(isopropoxycarbonyl)-L-cyclohexylalaninol (**3**) (0.98 g, 94%) as an oil; $[\alpha]_D^{23}$ −27.2° (*c* 1.06, $CHCl_3$); ν_{max} (neat) 1 680 cm^{-1} (CO); δ($CDCl_3$) 0.8–1.9 (19 H, m, cyclohexylmethyl H and Me_2), 3.4–3.9 (3 H, m, C*H*C*H*$_2$OH), 4.5–4.7 (1 H, m, NH), and 4.8–5.0 (1 H, m, C*H*Me_2) (FAB-MS, *m/z* 244 (*M* + 1). $C_{13}H_{25}NO_3$ requires *M* + 1, 244).

(2R,3S)-3-*Amino*-4-*cyclohexyl*-2-*hydroxybutyric Acid*·*HCl* (**4**).—To a stirred solution of the carbamate (**3**) (470 mg, 1.9 mmol), DMSO (1.4 ml, 19 mmol), and triethylamine (0.81 ml, 5.7 mmol) in benzene (0.7 ml) at 20–25 °C was added portionwise sulphur trioxide–pyridine complex (920 mg, 5.7 mmol). After 20 min, the mixture was poured into ice–water and extracted with $CHCl_3$ (20 ml). To the organic layer was added water (5 ml) followed, upon cooling to 0 °C, by NaCN (190 mg, 3.8 mmol) and 1M-HCl (3.8 ml, 3.8 mmol). After 3 h, the solvent ($CHCl_3$) was removed under reduced pressure and conc. HCl (13 ml) was added to the residue. The mixture was heated at 80 °C for 11 h and was then concentrated to *ca.* 15 ml. After storage overnight, (2R,3S)-3-*amino*-4-*cyclohexyl*-2-*hydroxybutyric acid*·*HCl* (**4**) [280 mg, 60% from (**3**)] was collected by filtration as white crystals; m.p. 172–175 °C (from water); $[\alpha]_D^{23}$ −11.2° (*c* 2.0, water); ν_{max}(KBr) 1 720 cm^{-1} (CO); δ(D_2O) 0.85–1.8 (13 H, m, cyclohexylmethyl H), 3.65–3.8 (1 H, m, 3-H), and 4.36 (1 H, d, *J* 3.3 Hz, 2-H) (Found: C, 50.2; H, 8.2; N, 5.9. $C_{10}H_{19}NO_3$·HCl requires C, 50.52; H, 8.48; N, 5.89%).

Isopropyl (2R,3S)-3-*Amino*-4-*cyclohexyl*-2-*hydroxybutyrate*·*HCl* (**5**).—A solution of the acid (**4**) (0.28 g, 1.2 mmol) in isopropyl alcoholic HCl (5 ml) was heated at 80 °C for 1 h. The solution was concentrated and the product was recrystallized from ethyl acetate (1 ml) to give *isopropyl* (2R,3S)-3-*amino*-4-*cyclohexyl*-2-*hydroxybutyrate*·*HCl* (**5**) (0.31 g, 95%) as white crystals; m.p. 118–119 °C (from EtOAc); $[\alpha]_D^{23}$ −7.4° (*c* 2.4, water); ν_{max}(KBr) 1 720 cm^{-1} (CO); δ(D_2O) 0.85–1.25 (5 H, m, cyclohexylmethyl H), 1.30 (6 H, d, *J* 6.6 Hz, Me_2), 1.35–1.8 (8 H, m, cyclohexylmethyl H), 3.6–3.75 (1 H, m, 3-H), 4.37 (1 H, d, *J* 5.0 Hz, 2-H), and 5.10 (1 H, quint, *J* 6.6 Hz, C*H*Me_2) (Found: C, 55.4; H, 9.1; N, 4.95. $C_{13}H_{25}NO_3$·HCl requires C, 55.80; H, 9.37; N, 5.01%).

Isopropyl (2R,3S)-4-*cyclohexyl*-2-*hydroxy*-3-{N-[(2R)-2-*morpholinocarbonylmethyl*-3-(1-*naphthyl*)*propionyl*]-L-*histidyl*}*aminobutyrate* (**1**).—To a stirred solution of compound (**8**)[13] (1.0 g, 1.8 mmol) in MeOH (10 ml) at 0 °C was added 1M-NaOH (2.2 ml, 2.2 mmol). After 2 h, the solution was gradually warmed to ambient temperature and was stirred overnight. 1M-HCl (2.2 ml, 2.2 mmol) was then added to the mixture and the solution was evaporated under reduced pressure. To a stirred mixture of the residue in dioxane (7 ml) and water (7 ml) at 0 °C were added triethylamine (0.25 ml, 1.8 mmol) and Boc_2O (390 mg, 1.8 mmol). After 2 h, the mixture was gradually warmed to ambient temperature, then stirred overnight,* and evaporated under reduced pressure. To a solution of the residue and compound (**5**) (0.5 g, 1.8 mmol) in MeCN (10 ml) at 0 °C were added triethylamine (0.25 ml, 1.8 mmol), HONB (0.32 g, 1.8 mmol), and DCC (0.37 g, 1.8 mmol). After 2 h, the mixture was gradually warmed to ambient temperature, stirred overnight, filtered, and evaporated under reduced pressure. The residue was dissolved in ethyl acetate and the solution was washed successively with aq. citric acid, 5% aq. $NaHCO_3$, and brine. PTSA monohydrate (0.34 g, 1.8 mmol) was added to the solution, which was then stirred at ~40 °C. Pure title compound (**1**) crystallized out of solution in the form of its PTSA salt. The crystals were filtered off, poured into 5% aq. $NaHCO_3$ (10 ml), and the mixture was extracted with $CHCl_3$ (5 ml × 3). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give *isopropyl* (2R,3S)-4-*cyclohexyl*-2-*hydroxy*-3-{N-[(2R)-2-*morpholinocarbonylmethyl*-3-(1-*naphthyl*)*propionyl*]-L-*histidyl*}*aminobutyrate* (**1**) (990 mg, 80%) as a white solid; m.p. 99–104 °C; $[\alpha]_D^{21.5}$ −28.6° (*c* 1.04, MeOH); ν_{max}(KBr) 1 735 (CO) and 1 635 cm^{-1} (CO); δ($CDCl_3$) 0.7–1.2 (5 H, m, cyclohexyl H), 1.23 (6 H, t, *J* 6.6 Hz, Me_2), 1.43 (2 H, t, *J* 7.1 Hz, cyclohexyl), 1.55–1.85 (6 H, m, cyclohexyl H), 2.3–2.8 (2 H, m, morpholinocarbonylCH_2), 3.0–3.7 (13 H, m, morpholino, naphthylCH_2C*H*, and imidazolylCH_2), 4.08 (1 H, d, *J* 2.2 Hz, cyclohexylnorstatine 2-H), 4.3–4.6 (2 H, m, histidine α-H and cyclohexylnorstatine 3-H). 5.02 (1 H, quint, *J* 6.6 Hz, C*H*Me_2), 6.83 (1 H, s, imidazole 5-H), 7.01 (1 H, d, *J* 9.3 Hz, NH), 7.28 (1 H, d, *J* 8.8 Hz, naphthalene 2-H), 7.25–7.55 (4 H, m, naphthalene 3-, 6-, and 7-H, and NH), 7.60 (1 H, s, imidazole 2-H), 7.74 (1 H, d, *J* 8.2 Hz, naphthalene 4-H), 7.85 (1 H, d, *J* 7.1 Hz, naphthalene 5-H), and 8.04 (1 H, d, *J* 7.7 Hz, naphthalene 8-H); HPLC 99.5% [column, YMC-Packed Column R-ODS-5, 4.6 × 250 mm; eluant acetonitrile–0.05M-aq. NH_4OAc (11:9); flow rate 1 ml min^{-1}; elution time 9.7 min]; FAB-MS *m/z* 690 (*M* + 1) (Found: C, 65.4; H, 7.5; N, 9.8. $C_{38}H_{51}N_5O_7 \cdot \frac{1}{2}H_2O$ requires C, 65.31; H, 7.50; N, 10.02%).

N-[(2R)-2-*Morpholinocarbonylmethyl*-3-(1-*naphthyl*)*propionyl*]-N^{im}-*Boc*-L-*histidine* (**10**).—Chloroform was added to the previously described mixture† and the solution was washed successively with aq. citric acid and brine, dried over $MgSO_4$, and evaporated to give N-[(2R)-2-*morpholinocarbonylmethyl*-3-(1-*naphthyl*)*propionyl*]-N^{im}-*Boc*-L-*histidine* (**10**) (85% yield) as a white solid; m.p. 88–92 °C; $[\alpha]_D^{22}$ +43.3° (*c* 0.50, MeOH); ν_{max}(KBr) 1 750 (CO) and 1 640 cm^{-1} (CO); δ($CDCl_3$) 1.60 (9 H, s, Bu^{t}O), 2.3–2.4 (1 H, m, morpholinocarbonylC*H*), 2.8–3.7 (14 H, m, morpholino, naphthylCH_2C*H*, imidazolylCH_2, and morpholinocarbonylC*H*), 4.45–4.6 (1 H, m, histidine α-H), 6.62 (1 H, d, *J* 6.0 Hz, NH), 7.2–7.5 (4 H, m, naphthalene 2-, 3-, 6-, and 7-H), 7.57 (1 H, s, imidazole 5-H), 7.72 (1 H, d, *J* 7.7 Hz, naphthalene 4-H), 7.83 (1 H, d, *J* 7.1 Hz, naphthalene 5-H), 8.07 (1 H, d, *J* 8.8 Hz, naphthalene 8-H), and 8.15 (1 H, s, imidazole 2-H); FAB-MS *m/z* 565 (*M* + 1) (Found: C, 61.8; H, 6.5; N, 9.2. $C_{30}H_{36}N_4O_7 \cdot \frac{1}{5}CHCl_3$ requires C, 61.64; H, 6.20; N, 9.52%).

* Compound (**10**) was isolated from this mixture. The procedure is described in the following section.

† This was obtained from the mixture produced in the synthesis of (**1**).

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