[Chem. Pharm. Bull.]
32(4)1373—1384(1984)

Synthesis of the Imidazo[1,2-*a*]indole-spirolactone Ring System by Oxidative Double Cyclization. A Synthetic Approach to Tryptoquivalines¹⁾

MASAKO NAKAGAWA,* MIKIKO SODEOKA, KEIICHI YAMAGUCHI,
and TOHRU HINO

Faculty of Pharmaceutical Sciences, Chiba University,
1-33 Yayoi-cho, Chiba 260, Japan

(Received July 29, 1983)

Imidazo[1,2-*a*]indole-spirolactone **13**, the principal ring system of tryptoquivalines, was successfully synthesized by a new method *via* oxidative double cyclization of 1-(*N*-alkoxycarbonylalanyl)-3-indolepropionic acids (**5**) with *N*-bromosuccinimide, which were synthesized by acylation of benzyl 3-indolepropionate (**10**) with *N*-alkoxycarbonyl alanine *p*-nitrophenyl ester (**12**). The use of KF, 18-crown-6 and (iso-Pr)₂NEt in acetonitrile lead to high yields of benzyl 1-(*N*-methoxycarbonyl- α -methylalanyl)-3-indolepropionates (**4**). The removal of the protecting group of **13c** provided **2**. The mechanisms of these reactions are discussed.

Keywords—tryptoquivaline; imidazo[1,2-*a*]indole-spirolactone; 1-(*N*-alkoxycarbonylalanyl)-3-indolepropionic acid; oxidative double cyclization; *N*-bromosuccinimide; acylation

The isolation and structure elucidation of about 14 tryptoquivalines, which are toxic and tremorgic mycotoxins obtained from *Aspergillus clavatus*²⁾ and *A. fumigatus*,³⁾ have been reported during the last ten years. These compounds typically contain the imidazo[1,2-*a*]indole-spirolactone ring system **2** shown in Chart 1.

One total synthesis⁴⁾ and a formal total synthesis⁵⁾ of **1b** have since been described. As a part of our investigations aimed at the synthesis of the unique heterocyclic skeleton of these mycotoxins, we report here a convenient synthesis of **2** which involves the double ring closure of N onto C₂ and of CO₂H onto C₃ in an intermediate **3** formed by way of a bromonium ion-initiated reaction of **5**.

Bromination of 3-alkylindole with *N*-bromosuccinimide (NBS) under ionic conditions has been shown to proceed *via* the 3-bromoindolenine intermediate **6a** which collapses either to 2-bromoindoles or to oxindoles depending on the reaction media.⁶⁾ We have reported that in the presence of pyridine, 3-methylindole⁷⁾ produced *N*-(2-indolyl) pyridinium salt by reaction with dioxane-dibromide. A similar result was obtained by bromination of 3-phenylindole.⁸⁾ Furthermore, the influence of a substituent at the *N*-position of indoles was studied and it was found that the bromination of *N*-acylindoles also proceeded in a similar manner *via* **6a** to give 2-halo derivatives and related compounds.⁹⁾ When a nucleophilic group was present at an appropriate position in the 3-substituents, the nucleophile in an aprotic solvent could attack the 2-position of the 3*H*-indolium intermediate to form a cyclic product **7** which was converted to the corresponding spirooxindoles **8** by further bromination,¹⁰⁾ whereas in a hydrolytic solvent, the spiro lactone derivative **9** was obtained from 3-indolepropionic acid and acyltryptophan.^{6a, b)}

Synthesis of the starting material **5** was envisaged *via* condensation of the corresponding amino acid with benzyl 3-indolepropionate followed by hydrogenolysis. The known method for acylation of indoles with an amino acid is the acylation of indole itself with the acid chloride, prepared from *N*-benzoxycarbonylglycine or β -alanine and PCl₅, in the presence of NaH in *N,N*-dimethylformamide (DMF).¹¹⁾ However, when we attempted a model synthesis

Chart 1

Chart 2

of benzyl 1-(*N*-methoxycarbonylglycyl)-3-indolepropionate (**4a**) from benzyl 3-indolepropionate (**10**) according to the reported conditions, **4a** was not formed. Instead, *N*-methoxycarbonylglycine benzyl ester (**11**) was obtained in 18% yield and the starting material **10** was recovered in 56% yield. The reaction of **10** with *N*-methoxycarbonylglycine *p*-nitrophenyl ester (**12a**) in the presence of NaH in DMF was then carried out under nitrogen and **4a** was obtained in 24% yield, together with a small amount of **11** and benzyl 1-methoxycarbonyl-3-indolepropionate. Treatment of **10** with *N*-methoxycarbonyl-methylalanine *p*-nitrophenyl ester (**12b**) under similar reaction conditions provided **4b** in 73% yield.

We next planned to examine the replacement of the strong base, NaH used to generate the indolide ion, in order to avoid racemization of the tryptophan ester; the second objective was to explore the possibility of improving the yield. Several other conditions, including the

use of tetra-*n*-butylammonium hydrogen sulfate as a phase transfer catalyst,¹²⁾ thallium (I) ethoxide,¹³⁾ or silylation with bis(trimethylsilyl)acetamide followed by treatment with **12** in the presence of tetramethylammonium chloride ($\text{Me}_4\text{N}^+\text{Cl}^-$),¹⁴⁾ were examined, and potassium fluoride (KF) with 18-crown-6 was chosen as the most appropriate system for further study since no racemization has been reported to occur during acylation of tryptophan derivatives.¹⁵⁾ Thus, the reaction of **10** with **12b** in acetonitrile in the presence of KF, 18-crown-6 and (iso-Pr)₂NEt at 60 °C for 35 h and at room temperature for a further 12.5 h gave **4b** in 84% yield and 12% of **10** was recovered. Likewise, **4c** was obtained in 51% yield by treatment of **10** with *N*-trichloroethoxycarbonylmethylalanine *p*-nitrophenyl ester (**12c**) under similar conditions. Debenzylation of **4a** and **4b** occurred smoothly in methanol upon hydrogenolysis on Pd/C to give the corresponding acids **5a** and **5b** in 98% and 93% yields, respectively. In contrast, the reaction of **4c** in methanol was sluggish; only 3% yield of the required acid **5c** was obtained and the methyl ester, **18c**, was formed in 75% yield in addition to the methyl ester of **5d** (6%). In ethyl acetate, however, **4c** was smoothly debenzylated to give **5c** in 75% yield.

With the requisite acid **5** in hand, we carried out the first series of transformations of **5a** to **13a** by halogenation. Initial attempts to obtain **13a** by treatment of **5a** with 1 equivalent of *N*-chlorosuccinimide (NCS) in acetic acid at 70–75 °C for 70 min failed and **14a** was obtained in 39% yield. Bromination of **5a** with NBS in acetic acid at ambient temperature did not give **13a** but **14a** was obtained. The reaction of **5a** with NBS (1 eq) either in *tert*-butanol or in methylene chloride gave **14b** as the only isolable product in 35% and 51% yields, respectively. Consequently, we decided to use **5b** as the starting material. By treatment with NBS (1 eq) in methylene chloride at ambient temperature for 50 min, **5b** was converted to a less polar unstable intermediate which gradually changed to **17b** (30%), **18b** (19%), and **19b** (9%) when left for 4.5 h at –10 ~ –20 °C and the cyclization product **13b** was not obtained. This intermediate was, however, successfully isolated by quick removal of succinimide with water followed by removal of the solvent, and was proved to be the bromo- δ -lactone **16b**. The proton nuclear magnetic resonance (¹H-NMR) spectrum of **16b** showed the methine proton PhNCH–O at δ 7.01 as a singlet with a significant downfield shift as compared with the corresponding proton in other non-acylated PhNCH–O or PhNCHN systems.¹⁶⁾ The infrared (IR) spectrum contained a sharp band at 1760 cm^{–1} assigned to the δ -lactone ring in addition to the amide carbonyl bands at 1720 sh and 1700 cm^{–1}, and the amide II band at 1520 cm^{–1}. The ultraviolet (UV) spectrum in ethanol displayed λ_{max} at 231, 254 sh, and 299.5 nm. The similar reaction of **5b** in 5% MeOH–CH₂Cl₂ at room temperature for 7 min showed essentially a single spot corresponding to **16b** on thin layer chromatography (TLC) and no other significant spot was detected. Work-up after a further 50 min of stirring provided **17b** (12%), **18b** (5%), **19b** (22%), and **20b** (38%) as a mixture of two stereoisomers. The foregoing evidence demonstrated that the products **17**, **18**, **19**, and **20** were formed from the common intermediate **16** by participation of a trace amount of methanol present in methylene chloride, and **17** was derived from **16** by dehydrobromination followed by further bromination as shown in Chart 3.

Other attempts to convert **16b** to **13b** under S_N1 conditions usually applicable to alkyl halides using Ag₂CO₃–CH₃CN, AgNO₃–CH₃CN, Ag₂O–DMF¹⁷⁾ or under basic conditions using NaH, Et₃N or K₂CO₃ failed. The desired product **13b** was finally prepared in 20% yield by bromination of **5b** with NBS (1 eq) in anhydrous methylene chloride at ambient temperature for 20 min (at this stage the reaction mixture showed essentially a single spot corresponding to **16b** on TLC and no other significant spot was detected) followed by 130 min of refluxing. It appeared that cyclization of **16b** to **13b** was difficult to drive to completion, some starting material (27%) being reformed on heating with liberation of bromine as well as other unwanted polar substances. By the use of 2 eq of NBS, the yield of **13b** was increased to

Chart 3

Fig. 1. Molecular Structure of 13b

43% when bromination was carried out in a refluxing solution of $\text{CHCl}_3\text{--CF}_3\text{CO}_2\text{H}$ (10:1). The structure of **13b** was confirmed by spectroscopic and elemental analysis. The IR spectrum of this compound showed no NH, CO_2H , or amide II bands but showed a γ -lactone band at 1790 cm^{-1} . In the $^1\text{H-NMR}$ spectrum the NCHN proton signal appeared at δ 5.62 as a singlet. Spectroscopic evidence, however, could not furnish information about the stereochemistry of **13b**. X-Ray analysis showed **13b** to have the *cis* configuration of the C–O and C–N bands, which is the same stereochemistry as in tryptoquivalines. An ORTEP drawing is shown in Fig. 1.

Under anhydrous conditions, **16b** was probably equilibrated with the acyl-3*H*-indolium ion **21b** which cyclized to *cis* and *trans* **13b** by the expected double cyclization. The failure to isolate the *trans* isomer of **13b** suggested that *cis* **13b** was probably the thermodynamically more stable isomer, and the less stable *trans* isomer **13b** appeared to revert to *cis* **13b** via **22** under the reaction conditions used. In order to improve the yield of **13b**, other reaction conditions were examined. All our attempts to effect intramolecular double cyclization with NBS using other solvents such as tetrahydrofuran (THF), benzene, and DMF resulted in either decomposition of the intermediate or recovery of the starting material and a small amount of **13b** was formed only when NBS or *N*-iodosuccinimide (NIS) in CH_3CN was used.

Removal of the methoxycarbonyl group of **13b** was then attempted by treatment with excess trimethylsilyl iodide¹⁸⁾ or $\text{MeSmE--MeSO}_3\text{H}$,¹⁹⁾ but under both conditions the γ -lactone ring was preferentially cleaved to give **23**. Therefore, the approach to **2** via **13b** was abandoned and next we turned to the cyclization of **5c**. In a manner identical with the foregoing, bromination of **5c** in methylene chloride resulted in exclusive formation of **16c** which, in contrast to **16b**, was resistant to further cyclization by refluxing. However, when NBS (2 eq) was added to a boiling solution of **5c** in $\text{CF}_3\text{CO}_2\text{H--CH}_2\text{Cl}_2$ (1:10), **13c** was obtained in 29% yield. Attempted cyclization of **5c** to **13c** under other reaction conditions failed except when NIS in MeCN was used or when TFA was added to **16c** in methylene chloride, in which cases small amounts of **13c** were obtained. Deprotection of the trichloroethoxycarbonyl group of **13c** was effected by treatment with Zn in acetic acid to afford the desired product **2**. The $^1\text{H-NMR}$ spectrum of **2** in dimethyl sulfoxide (DMSO) showed the PhNCHN proton at δ 5.37 as a doublet corresponding to that of tryptoquivalines G (δ 5.30).⁴⁾ The other spectral data supported the structure of **2**. Further confirmation was obtained by converting **2** to **13b** with methyl chloroformate in the presence of K_2CO_3 , demonstrating that **13c** and **2** have the same stereochemistry as **13b**. Recently we have succeeded in the synthesis of (+)- and (–)-tryptoquivalines G and L by applying the present method.¹⁾ A further extension of this approach to the synthesis of optically active tryptoquivaline itself is under way.

Experimental

Melting points were measured with Yamato MP-1 and Yanagimoto micro melting point apparatus, and are uncorrected. UV spectra were recorded with Hitachi 323 and 340 spectrophotometers. IR spectra were obtained with Hitachi 295 and 260 instruments, and mass spectra (MS) with Hitachi RMU-7M and M-60 mass spectrometers. NMR spectra were run on JEOL MH-100 and FX-270 spectrometers, with SiMe_4 as an internal standard. Chemical shifts are given as δ values (ppm). Unless otherwise noted, electronic spectra (λ in nm) refer to solutions in 95% EtOH, IR spectra (ν in cm^{-1}) to KBr disks, and NMR spectra to solutions in CDCl_3 .

Benzyl 3-Indolepropionate (10)—A solution of 3-indolepropionic acid (30.0 g, 159 mmol), benzyl alcohol (34.3 g, 318 mmol), and *p*-toluenesulfonic acid monohydrate (1.5 g, 8 mmol) in benzene (180 ml) was refluxed under a Dean-Stark trap for 2 h under N_2 . The reaction mixture was then diluted with benzene (170 ml) and the aqueous solution was extracted with benzene. The combined organic layer was washed with NaHCO_3 solution, and water, and dried over anhydrous Na_2SO_4 . Evaporation of the solvent gave a residue, which was crystallized from methanol to give **10** (15.1 g, mp $69\text{--}70^\circ\text{C}$). The mother liquor was evaporated and the residue was purified by column chromatography on alumina (200 g, benzene) followed by crystallization from methanol to give **10** (13 g). Excess

benzyl alcohol contained in the mother liquor was removed *in vacuo* and the residue was chromatographed on silica gel (120 g, CH_2Cl_2) followed by crystallization from methanol to give the third crop of **10** (7.3 g). Total yield of **10**, 35.4 g (79.9%), mp 70–71 °C. UV λ_{max} (ϵ): 220.5 (35400), 274 sh (5600), 281 (6000), 289.5 (5100). IR ν_{max} : 3310, 3050 (NH), 1726 (CO). $^1\text{H-NMR}$ (100 MHz): 2.72 (2H, t, $J=8$ Hz, CH_2CO), 3.09 (2H, t, $J=8$ Hz, CH_2), 5.07 (2H, s, CH_2Ph), 6.85 (1H, d, $J=3$ Hz, $\text{C}_2\text{-H}$), 6.90–7.40 (8H, m, arom. H), 7.40–7.62 (1H, m, arom. H), 7.82 (1H, brs, NH, exchangeable). $^{13}\text{C-NMR}$ (67.8 MHz): 20.65 (t, CH_2), 34.96 (t, CH_2CO), 66.20 (t, CH_2Ph), 111.12 (d, C-7), 114.72 (s, C-3), 118.66, 119.29 (d, C-4, C-5), 121.48, 122.00 (d, C-2, C-6), 127.13 (s, C-3a), 128.13, 128.48 (d, Ph), 135.97 (s, Ph), 136.25 (s, C-7a), 173.23 (s, CO). *Anal.* Calcd for $\text{C}_{18}\text{H}_{17}\text{NO}_2$: C, 77.39; H, 6.13; N, 5.01. Found: C, 77.51; H, 6.19; N, 4.99.

***N*-Methoxycarbonylglycine *p*-Nitrophenyl Ester (**12a**)**—Dicyclohexylcarbodiimide (DCC) (10.1 g, 49 mmol) in CH_2Cl_2 (25 ml) was added dropwise to a stirred solution of *N*-methoxycarbonylglycine (6.65 g, 50 mmol) and *p*-nitrophenol (6.96 g, 50 mmol) in CH_2Cl_2 (100 ml) over a period of 70 min. After a further 30 min of stirring at room temperature, the reaction mixture was filtered to remove dicyclohexylurea (DCU). The filtrate was evaporated to give a pale yellow solid (13.76 g), which was dissolved in a small amount of hot acetone, and insoluble DCU was removed by filtration. The filtrate was concentrated followed by crystallization of the residue from CH_2Cl_2 –ether–hexane to give **12a** (11.28 g, 88.8%) as pale yellow prisms, mp 92.5–93.5 °C. UV λ_{max} (ϵ): 211.5 sh (9600), 267 (10500). IR ν_{max} : 3460, 3320, 3100, 3070 (NH), 1780, 1760 sh, 1730, 1716 sh, 1693 (CO), 1540 (NO_2), 1518 (amide II band), 1342 (NO_2). $^1\text{H-NMR}$ (100 MHz): 3.75 (3H, s, OMe), 4.25 (2H, d, $J=7$ Hz, CH_2), 5.40 (1H, brs, NH), 7.30 (2H, d, $J=9$ Hz), 8.25 (2H, d, $J=9$ Hz). *Anal.* Calcd for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_6$: C, 47.25; H, 3.97; N, 11.02. Found: C, 47.29; H, 3.97; N, 11.07.

Benzyl 1-(*N*-Methoxycarbonylglycyl)-3-indolepropionate (4a**)**—A solution of **10** (3.050 g, 12 mmol) in DMF (10 ml) was added to a stirred suspension of NaH (612 mg, 12 mmol) in dry DMF (30 ml) with ice–salt cooling under N_2 . The solution was stirred at –10 to –15 °C for 100 min, then *p*-nitrophenylester **12a** (3.048 g, 12 mmol) in DMF (10 ml) was added to the reaction mixture, and the whole was stirred for 20 min. Removal of DMF *in vacuo* gave a solid which was extracted with anhydrous CH_2Cl_2 to remove sodium *p*-nitrophenyl ester. The extract was filtered and the filtrate was concentrated to give a residue (5.8 g) which was column chromatographed on silica gel (150 g, benzene–acetone, 7:1). First elution gave benzyl 1-methoxycarbonyl-3-indolepropionate (76 mg). Second elution with the same solvent gave a mixture of benzyl 1-methoxycarbonyl-3-indolepropionate and **10** (956 mg); this mixture was rechromatographed twice on silica gel (50 g, benzene–acetone, 10:1, 12:1) to give benzyl 1-methoxycarbonyl-3-indolepropionate (134 mg) (totaling 210 mg, 5.2%) and **10** (787 mg). Third elution with the same solvent gave **10** (276 mg). Fourth elution gave a mixture of **10**, **4a**, and *p*-nitrophenol (941 mg); this mixture was separated by chromatography on silica gel (50 g, benzene–acetone, 7:1) to give **10** (456 mg; total 1520 mg, 45.4%) and crude **4a** (476 mg). Fifth elution provided crude **4a** (1299 mg). The crude **4a** was purified on Sephadex LH 20. Elution with methanol provided **4a** (1132 mg, 23.9%) and **11** (303 mg, 11.2%). Recrystallization of **4a** from methanol gave colorless needles, mp 97.5–98.5 °C. UV λ_{max} (ϵ): 241 (18900), 263 sh (8700), 273 sh (7000), 292 (6700), 301 (7000). IR ν_{max} : 3385, 3330 (NH), 3125, 3055, 3030, 1740 (CO), 1732 (NHCO), 1715 (NCO), 1540 (amide II band). $^1\text{H-NMR}$ (100 MHz): 2.75 (2H, t, $J=6$ Hz, CH_2CO), 3.04 (2H, t, $J=6$ Hz, CH_2), 3.74 (3H, s, OMe), 4.42 (2H, d, $J=6$ Hz, N-CH_2), 5.11 (2H, s, CH_2Ph), 5.62 (1H, brs, NH), 7.09 (1H, s, $\text{C}_2\text{-H}$), 7.20–7.60 (8H, m, arom. H), 8.35 (1H, dd, $J=8$ and 2 Hz, $\text{C}_7\text{-H}$). MS m/z (%): 394 (26) M^+ , 279 (70), 188 (100), 130 (42), 91 (48). *Anal.* Calcd for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 66.96; H, 5.64; N, 7.08.

***N*-Methoxycarbonyl- α -methylalanine**—Methyl chloroformate (45.4 g, 0.48 mol) and 4N NaOH (120 ml) were added dropwise simultaneously to a vigorously stirred solution of α -methylalanine (25.0 g, 0.24 mol) in 4N NaOH (60 ml) with ice-cooling over a period of 15 min. The reaction mixture was stirred for 2 h under ice-cold conditions, then basified with 10% NaOH and washed with CH_2Cl_2 (40 ml $\times$ 5). The aqueous layer was acidified with conc. HCl to pH 1 and extracted with MeCO_2Et (500 ml, 300 ml $\times$ 2). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to leave crude *N*-methoxycarbonyl- α -methylalanine (31.89 g, 81.7%) as colorless crystals. Recrystallizations from methanol afforded colorless prisms, mp 157–158 °C (28.50 g, 72.9%). IR ν_{max} : 3330, 3065 (NH, OH), 1737 (CO_2H), 1673 (CONH), 1548 (amide II band). $^1\text{H-NMR}$ (100 MHz, $\text{DMSO}-d_6$): 1.32 (6H, s, Me), 3.50 (3H, s, OMe), 7.32 (1H, s, NH, exchangeable), 12.2 (1H, brs, OH, exchangeable). MS m/z (%): 146 (2) M^+ – 15, 116 (8), 42 (100). *Anal.* Calcd for $\text{C}_6\text{H}_{11}\text{NO}_4$: C, 44.71; H, 6.88; N, 8.69. Found: C, 44.78; H, 6.84; N, 8.68.

***N*-2,2,2-Trichloroethoxycarbonyl- α -methylalanine**—2,2,2-Trichloroethyl chloroformate (0.69 ml, 5 mmol) was added to a solution of α -methylalanine (1.03 g, 10 mmol) in aqueous NaOH (0.4 g, 10 mmol/ H_2O , 5 ml) with ice-cooling. The reaction mixture was stirred for 1.5 h (pH 7–8), then NaOH (0.2 g, 5 mmol) in H_2O (1 ml) and 2,2,2-trichloroethyl chloroformate (0.69 ml, 5 mmol) were added and the reaction mixture was stirred for a further 50 min under ice-cooling. Trichloroethyl chloroformate (0.69 ml, 5 mmol) and NaOH (0.2 g) in H_2O (1 ml) were again added, and the whole was stirred for 1 h, then basified to pH 10 with NaOH solution and washed with CH_2Cl_2 (15 ml, 10 ml). The aqueous layer was acidified with conc. HCl to pH 1 and extracted with $\text{CH}_3\text{CO}_2\text{Et}$ (25 ml, 20 ml $\times$ 4). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated to give crude *N*-2,2,2-trichloroethoxycarbonyl- α -methylalanine (1.679 g, 60.3%) as colorless crystals. Recrystallization from methanol afforded colorless prisms, mp 152–155.5 °C. IR ν_{max} : 3295, 3140, 3050 (NH, OH), 1738, 1703 (CO), 1540 (amide II band), 730 (C–Cl). $^1\text{H-NMR}$ (100 MHz, $\text{DMSO}-d_6$): 1.38 (6H, s, Me), 4.74 (2H, s, CH_2), 7.89 (1H, s, NH,

exchangeable), 12.21 (1H, brs, COOH, exchangeable). *Anal.* Calcd for $C_7H_{10}Cl_3NO_4$: C, 30.18; H, 3.62; N, 5.03. Found: C, 30.25; H, 3.59; N, 5.06.

***N*-Methoxycarbonyl- α -methylalanine *p*-Nitrophenyl Ester (12b)**—DCC (25 g, 0.12 mol) in CH_2Cl_2 (75 ml) was added to a solution of *N*-methoxycarbonyl- α -methylalanine (19.71 g, 0.12 mol) and *p*-nitrophenol (17.01 g, 0.12 mol) in CH_2Cl_2 (250 ml) over a period of 1 h at 21 °C. After stirring of the mixture for 160 min, precipitates (DCU) were filtered off. Evaporation of the filtrate gave a pale yellow solid (24.51 g) which was dissolved in hot acetone, and the insoluble DCU was filtered. Crystallization of the residue obtained by evaporation of the filtrate from acetone or acetone–methylene chloride afforded **12b** (28.76 g, 85.8%) as pale yellow prisms or as needles, mp 111–112 °C. UV λ_{max} (ϵ): 210 sh (9600), 267 (10600). IR ν_{max} : 3315 (NH), 1780 (CO₂), 1700 (CONH), 1528 (amide II band and NO₂), 1349 (NO₂). ¹H-NMR (100 MHz): 1.67 (6H, s, Me), 3.71 (3H, s, OMe), 5.31 (1H, s, NH, exchangeable), 7.30 (2H, d, *J* = 9 Hz, arom. H), 8.27 (2H, d, *J* = 9 Hz, arom. H). MS *m/z* (%): 144 (13), 116 (100), 84 (100), 73 (16), 72 (30), 56 (43). *Anal.* Calcd for $C_{12}H_{14}N_2O_6$: C, 51.06; H, 5.00; N, 9.93. Found: C, 51.11; H, 4.99; N, 9.94.

***N*-(2,2,2-Trichloroethoxy)carbonyl- α -methylalanine *p*-Nitrophenyl Ester (12c)**—DCC (5.106 g, 25 mmol) in CH_2Cl_2 (15 ml) was added to a stirred solution of *N*-(2,2,2-trichloroethoxy)carbonyl- α -methylalanine (6.925 g, 25 mmol) and *p*-nitrophenol (3.475 g, 25 mmol) in CH_2Cl_2 (100 ml) over a period of 80 min. The reaction mixture was stirred for 1.5 h and filtered. The filtrate was evaporated *in vacuo* to leave a residue which was treated with a small amount of hot acetone. The insoluble DCU was filtered off. The filtrate was evaporated and the residue was crystallized from acetone–methylene chloride to give **12c** (9.036 g, 90.9%) as colorless prisms. Recrystallization from acetone gave mp 144–145.5 °C. UV λ_{max}^{ether} (ϵ): 209 sh (9150), 266 (10000). IR ν_{max} : 3320 (NH), 1766 (CO), 1720 (CONH), 1530 (amide II band and NO₂), 1348 (NO₂), 735 (C–Cl). ¹H-NMR (100 MHz): 1.70 (6H, s, Me), 4.73 (2H, s, OCH₂), 5.56 (1H, s, NH), 7.26 (2H, d, *J* = 9 Hz, arom. H), 8.26 (2H, d, *J* = 9 Hz, arom. H). *Anal.* Calcd for $C_{13}H_{13}Cl_3N_2O_6$: C, 39.07; H, 3.28; N, 7.01. Found: C, 39.56; H, 3.38; N, 7.10.

Benzyl 1-(*N*-Methoxycarbonyl- α -methylalanyl)-3-indolepropionate (4b)—1) A solution of **12b** (274 mg, 1 mmol) in DMF (4 ml) was added dropwise to a stirred suspension of NaH (51 mg, 1 mmol) in DMF (4 ml) with ice–salt cooling under N₂. After a further 15 min of stirring, the solvent was distilled off *in vacuo* and the residue was extracted with CH_2Cl_2 . The insoluble material (sodium *p*-nitrophenolate) was filtered off. The filtrate was evaporated and the residue was column-chromatographed on silica gel (20 g, benzene–acetone, 7:1) to give **4b** (305 mg, 72.7%). Recrystallization from methanol gave colorless needles, mp 125–126 °C. UV λ_{max} (ϵ): 243 (18900), 265 sh (8700), 273 sh (7300), 293 (6650), 301 (7200). IR ν_{max} : 3360 (NH), 1730, 1685 (CO), 1518 (amide II band). ¹H-NMR (270 MHz): 1.65 (6H, s, Me), 2.76 (2H, t, *J* = 7 Hz, CH₂CO), 3.05 (2H, t, *J* = 7 Hz, CH₂), 3.57 (3H, s, OMe), 5.11 (2H, s, CH₂Ph), 5.17 (1H, s, NH, exchangeable), 7.24–7.50 (7H, m, arom. H), 7.49 (1H, d, *J* = 8 Hz, C₄–H), 7.71 (1H, s, C₂–H), 8.54 (1H, d, *J* = 8 Hz, C₇–H). ¹³C-NMR (67.8 MHz): 20.36 (t, CH₂), 26.58 (q, Me $\times$ 2), 33.92 (t, CH₂CO), 52.38 (q, OMe), 58.54 (s, OC–C–NH), 66.31 (t, CH₂Ph), 117.65 (d, C-7), 118.26 (d, C-4), 120.68 (s, C-3), 122.12 (d, C-2), 123.56 (d, C-5), 125.46 (d, C-6), 128.05, 128.25, 128.59 (d, Ph), 129.29 (s, C-3a), 135.85 (s, Ph), 137.23 (s, C-7a), 155.26 (s, NHCO₂), 171.47 (s, NCO), 172.62 (s, CO₂CH₂Ph). MS *m/z* (%): 390 (15), 188 (77), 84 (100). *Anal.* Calcd for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63. Found: C, 68.18; H, 6.20; N, 6.59.

2) 18-Crown-6 (1.32 g, 5 mmol) was placed in a flask, followed by acetonitrile (20 ml) in which **10** (1.395 g, 5 mmol), **12b** (1.505 g, 5.5 mmol), and diisopropylethylamine (0.95 ml, 6 mmol) had been dissolved. Then dry potassium fluoride (0.58 g, 10 mmol, pre-dried over P₂O₅ for 15 h at 120 °C) was added. The suspension was stirred with protection from light for 5.5 h at 60 °C and then the solvent was removed *in vacuo*. The residue was column-chromatographed on neutral alumina (50 g, upper layer) and silica gel (70 g, lower layer). Elution with CH_2Cl_2 gave crude **4b** (1.765 g, 83.6%) and some **10** (173 mg, 12.4%) was recovered. Recrystallization of **4b** from methanol gave colorless needles (1.588 g, 75.3%), mp 126–127 °C.

Benzyl 1-(*N*-(2,2,2-Trichloroethoxy)carbonyl- α -methylalanyl)-3-indolepropionate (4c)—The reaction was carried out by a procedure similar to that for **4b** using 18-crown-6 (3.96 g, 15 mmol) in acetonitrile (60 ml), **10** (4.17 g, 15 mmol), **12c** (7.196 g, 18 mmol), EtN (iso-Pr)₂ (2.8 ml, 18 mmol), and KF (1.74 g, 30 mmol). The reaction mixture was refluxed for 19.5 h. Work-up was followed by purification through column chromatography (neutral alumina 130 g, upper layer; silica gel 150 g, lower layer; CH_2Cl_2 –hexane, 2:1 and CH_2Cl_2) and rechromatography on silica gel (150 g, hexane–ethyl acetate, 4:1) to give crude **4c** (4.059 g, 50.5%). Recrystallization from methanol gave colorless prisms, mp 96.5–97.5 °C. UV λ_{max} (ϵ): 242 (18500), 263 sh (8800), 273 sh (6900), 292 (6500), 301 (7000). IR ν_{max} : 3290 (NH), 1740, 1715 (CO), 1538 (amide II band). ¹H-NMR (270 MHz): 1.69 (6H, s, Me), 2.77 (2H, t, *J* = 7.5 Hz, CH₂CO), 3.03 (2H, t, *J* = 7.5 Hz, CH₂), 4.62 (2H, s, CH₂CCl₃), 5.12 (2H, s, CH₂Ph), 5.62 (1H, s, NH, exchangeable), 7.25–7.42 (2H, m, C₅–H, C₆–H), 7.26 (5H, s, Ph), 7.49 (1H, dd, *J* = 8 and 1 Hz, C₄–H), 8.53 (1H, d, *J* = 8 Hz, C₇–H), 7.64 (1H, s, C₂–H). ¹³C-NMR (67.8 MHz): 20.33 (t, CH₂), 26.32 (q, Me $\times$ 2), 33.83 (t, CH₂CO), 58.77 (s, CO–C–NH), 66.31 (t, CH₂Ph), 74.38 (t, CH₂CCl₃), 95.37 (s, CCl₃), 117.6 (d, C-7), 118.31 (d, C-4), 120.96 (s, C-3), 121.91 (d, C-2), 123.73 (d, C-5), 125.63 (d, C-6), 127.99, 128.28, 128.68 (d, Ph), 129.23 (s, C-3a), 135.88 (s, Ph), 137.17 (s, C-7a), 152.69 (s, NHCO₂), 170.86 (s, NCO), 172.59 (s, CO₂CH₂Ph). MS *m/z* (%): 390 (26), 299 (29), 188 (100), 91 (43), 84 (57). *Anal.* Calcd for $C_{25}H_{25}Cl_3N_2O_5$: C, 55.62; H, 4.67; N, 5.19. Found: C, 55.64; H, 4.65; N, 5.21.

1-(*N*-Methoxycarbonylglucyl)-3-indolepropionic Acid (5a)—A mixture of **4a** (1.97 g, 5 mmol), 5% Pd/C (180 mg) and methanol (600 ml) was stirred under a stream of hydrogen at room temperature for 5.5 h. After removal

of the catalyst by filtration, the solvent was removed *in vacuo*. The solid (1504 g) was washed with a small amount of methanol to give the crude acid **5a** (1.482 g, 97.5%) as a powder. Crystallization from methanol gave mp 183.5—185 °C. UV λ_{max} (ϵ): 240 (19400), 262 sh (8800), 271 sh (7200), 291 (6800), 299.5 (7100). IR ν_{max} : 3410 (NH), 3000—2500 (COOH), 1715, 1700 (CO), 1521 (amide II band). $^1\text{H-NMR}$ (100 MHz, DMSO- d_6): 2.66 (2H, t, $J=7$ Hz, CH_2CO), 2.94 (2H, t, $J=7$ Hz, CH_2), 3.60 (3H, s, OMe), 4.46 (2H, d, $J=7$ Hz, CH_2N), 7.20—7.45 (2H, m, arom. H), 7.45—7.75 (2H, m, arom. H), 7.72 (1H, s, NH, exchangeable), 8.30 (1H, d, $J=7$ Hz, $\text{C}_7\text{-H}$). MS m/z (%): 304 (29) M^+ , 272 (17), 189 (96), 130 (100). *Anal.* Calcd for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_5$: C, 59.20; H, 5.30; N, 9.21. Found: C, 59.31; H, 5.38; N, 9.07.

1-(*N*-Methoxycarbonyl- α -methylalanyl)-3-indolepropionic Acid (5b**)**—By the procedure just described, **4b** (2.532 g, 6 mmol) afforded **5b** (1.856 g, 93.3%). Recrystallization from methanol gave colorless prisms, mp 216—217 °C. UV λ_{max} (ϵ): 243 (18500), 265 sh (8500), 274 sh (7000), 293 (6500), 301 (7000). IR ν_{max} : 3435 (NH), 3000—2500 (COOH), 1710 (CO), 1500 (amide II band). $^1\text{H-NMR}$ (100 MHz, DMSO- d_6): 1.76 (6H, s, Me), 2.62 (2H, t, $J=7$ Hz, CH_2CO), 2.92 (2H, t, $J=7$ Hz, CH_2), 3.45 (3H, s, OMe), 7.10—7.46 (2H, m, $\text{C}_5\text{-H}$, $\text{C}_6\text{-H}$), 7.60 (1H, dd, $J=7$ and 2 Hz, $\text{C}_4\text{-H}$), 7.90 (1H, s, $\text{C}_2\text{-H}$), 8.15 (1H, s, NH, exchangeable), 8.20 (1H, dd, $J=7$ and 2 Hz, $\text{C}_7\text{-H}$), 12.15 (1H, br s, COOH, exchangeable). MS m/z (%): 332 (1) M^+ , 300 (30), 189 (80), 130 (100), 84 (59). *Anal.* Calcd for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_5$: C, 61.43; H, 6.07; N, 8.43. Found: C, 61.41; H, 6.12; N, 8.45.

1-(*N*-(2,2,2-Trichloroethoxy)carbonyl- α -methylalanyl)-3-indolepropionic Acid (5c**)**—1) By analogy with the procedure for the preparation of **5a**, a solution of **4c** (2.68 g, 5 mmol) in ethyl acetate (75 ml) was hydrogenated over 10% Pd/C (250 mg) for 8 h and **5c** (1.704 g, 74.8%) was obtained. Recrystallization from methanol gave colorless prisms, mp 201—202 °C. UV λ_{max} (ϵ): 242 (18400), 263 (8700), 273 sh (6900), 293 (6400), 301 (6900). IR ν_{max} : 3320, 3296 (NH), 3140, 3045, 3000—2500 (COOH), 1725 (CO), 1525 (amide II band). $^1\text{H-NMR}$ (270 MHz, DMSO- d_6): 1.60 (6H, s, Me), 2.63 (2H, t, $J=8$ Hz, CH_2CO), 2.85 (2H, t, $J=8$ Hz, CH_2), 4.68 (2H, s, CH_2CCl_3), 7.26 (1H, t, $J=7$ Hz, $\text{C}_5\text{-H}$), 7.32 (1H, t, $J=7$ Hz, $\text{C}_6\text{-H}$), 7.55 (1H, dd, $J=7$ and 1.5 Hz, $\text{C}_4\text{-H}$), 7.85 (1H, s, $\text{C}_2\text{-H}$), 8.36 (1H, d, $J=7$ Hz, $\text{C}_7\text{-H}$), 8.81 (1H, s, NH, exchangeable). MS m/z (%): 300 (39), 189 (39), 130 (100), 84 (67). *Anal.* Calcd for $\text{C}_{18}\text{H}_{19}\text{Cl}_3\text{N}_2\text{O}_5$: C, 48.07; H, 4.26; N, 6.23. Found: C, 48.25; H, 4.27; N, 6.25.

2) A solution of **4c** (2.678 g, 5 mmol) in methanol was hydrogenated over 5% Pd/C (330 mg) for 11.5 h and left overnight. The reaction mixture was filtered and the filtrate was evaporated to give a residue (2.428 g), which was column-chromatographed on silica gel (75 g, benzene–acetone, 5:1, 2:1) to give **18c** (1.757 g, 74.6%) and the methyl ester of **5d** (109 mg, 6.1%) and **5c** (69 mg, 3.1%). Methyl 1-(*N*-(2,2,2-trichloroethoxy)carbonyl- α -methylalanyl)-3-indolepropionate (**18c**), crystallized from acetone– CH_2Cl_2 –hexane, mp 100—103 °C, colorless prisms, UV λ_{max} : 243, 265 sh, 273 sh, 293, 302. IR ν_{max} : 3310 (NH), 1730, 1698 (CO), 1520 (amide II band). $^1\text{H-NMR}$ (100 MHz): 1.76 (6H, s, Me), 2.70 (2H, t, $J=7$ Hz, CH_2CO), 3.00 (2H, t, $J=7$ Hz, CH_2), 3.65 (3H, s, OMe), 4.60 (2H, s, CH_2CCl_3), 5.87 (1H, s, NH, exchangeable), 7.10—7.50 (3H, m, arom. H), 7.68 (1H, s, $\text{C}_2\text{-H}$), 8.50 (1H, dd, $J=8$ and 2 Hz, $\text{C}_7\text{-H}$). $^{13}\text{C-NMR}$ (67.8 MHz): 20.34 (t, CH_2), 26.33 (q, Me $\times 2$), 33.58 (t, CH_2CO), 51.74 (q, OMe), 58.83 (s, CO–C–NH), 74.34 (t, CH_2CCl_3), 95.37 (s, CCl_3), 117.61 (d, C-7), 118.29 (d, C-4), 121.00 (s, C-3), 121.87 (d, C-2), 123.70 (d, C-5), 125.62 (d, C-6), 129.22 (s, C-3a), 137.15 (s, C-7a), 152.76 (s, NHCO_2Me), 170.90 (s, NCO), 173.26 (s, CO_2). MS m/z (%): 466 (0.2) $\text{M}^+ + 4$, 464 (0.5) $\text{M}^+ + 2$, 462 (0.6) M^+ , 315 (11), 314 (49), 203 (56), 130 (100), 84 (68). The aromatic ring $^{13}\text{C-NMR}$ signals were assigned by the selective decoupling method. Methyl 1-(*N*-ethoxycarbonyl- α -methylalanyl)-3-indolepropionate, crystallized from CHCl_3 –hexane, mp 118.5—119.5 °C, colorless prisms. UV λ_{max} : 243, 265 sh, 274 sh, 292.5, 301.5. IR ν_{max} : 3320 (NH), 1698 (CO), 1520 (amide II band). $^1\text{H-NMR}$ (270 MHz, taken at 55 °C): 1.06 (3H, br s, CH_2CH_3), 1.71 (6H, s, Me), 2.69 (2H, t, $J=7$ Hz, CH_2CO), 3.02 (2H, t, $J=7$ Hz, CH_2), 3.67 (3H, s, OMe), 3.99 (2H, q, $J=7$ Hz, OCH_2CH_3), 5.11 (1H, s, NH, exchangeable), 7.23—7.40 (2H, m, $\text{C}_5\text{-H}$ and $\text{C}_6\text{-H}$), 7.47 (1H, d, $J=8$ Hz, $\text{C}_4\text{-H}$), 7.73 (1H, s, $\text{C}_2\text{-H}$), 8.51 (1H, d, $J=8$ Hz, $\text{C}_7\text{-H}$). MS m/z (%): 360 (2) M^+ , 314 (18), 203 (70), 142 (12), 130 (100).

Reaction of 5a with NCS in AcOH—NCS (20 mg, 0.15 mmol) in AcOH (3 ml) was added dropwise to a stirred solution of **5a** (46 mg, 0.15 mmol) in AcOH (5 ml) over a period of 10 min at 70 °C. The reaction mixture was stirred for 1 h at 75 °C and the solvent was removed *in vacuo*. The residue was column-chromatographed on alumina (2 g, benzene–acetone, 2:1) to give **14a** (21 mg, 39%). UV λ_{max} : 244, 273, 287. IR ν_{max} : 3350 (NH), 1780 (γ -lactone), 1700 (CO), 1525 (amide II band). $^1\text{H-NMR}$ (100 MHz): 2.12 (3H, s, MeCO_2), 2.20—3.10 (4H, m, CH_2CH_2), 3.71 (3H, s, OMe), 3.90—4.50 (2H, br s, NCH_2), 5.62 (1H, br s, NH), 6.60 (1H, s, $\text{C}_2\text{-H}$), 7.00—7.60 (3H, m, arom. H), 8.06 (1H, br s, $\text{C}_7\text{-H}$). MS m/z (%): 362 (12) M^+ , 247 (70), 205 (100), 159 (15), 148 (19), 145 (17), 88 (22).

Reaction of 5a with NBS in CH_2Cl_2 —NBS (27 mg, 0.15 mmol) in CH_2Cl_2 (10 ml) was added to a suspension of **5a** (46 mg, 0.15 mmol) in CH_2Cl_2 (20 ml) at room temperature and the reaction mixture was stirred for 110 min until it became a homogeneous solution and the starch-KI test became negative. The solvent was evaporated off and the residue was purified by preparative TLC (silica gel, 20 g, benzene–acetone, 2:1) to give **14b** (24 mg, 51%). UV λ_{max} : 248, 282, 291 sh. IR ν_{max} : 3350 (NH, OH), 1770 (γ -lactone), 1700 (CO), 1530 (amide II band). $^1\text{H-NMR}$ (100 MHz): 2.20—3.20 (4H, m, CH_2CH_2), 3.65 (3H, s, OMe), 4.20 and 4.35 (2H, d $\times 2$, $J=6$ Hz, CH_2N), 5.68 and 5.76 (1H, s $\times 2$, $\text{C}_2\text{-H}$), 6.10 (1H, br s, NH, exchangeable), 7.00—7.60 (3H, m, arom. H), 8.08 (1H, d, $J=8$ Hz, $\text{C}_7\text{-H}$). MS m/z (%): 320 (22) M^+ , 233 (31), 205 (100), 187 (46), 176 (34), 159 (25), 148 (59), 146 (50), 145 (88), 116 (33), 88 (61).

Reaction of 5a with NBS in *tert*-BuOH—A solution of NBS (27 mg, 0.15 mmol) in *tert*-BuOH (7 ml) was added

to a suspension of **5a** (46 mg, 0.15 mmol) in *tert*-BuOH (10 ml) at 28–30 °C. The reaction mixture was stirred for 40 min, and the solvent was removed *in vacuo*. The residue was subjected to preparative TLC (silica gel, 20 g, benzene–acetone, 2 : 1) to give **14b** (17 mg, 35%) as the only isolable product.

3-Methoxycarbonyl-2,2-dimethyl-1-oxo-2,3,3a,4-tetrahydro-1*H*-imidazo[1,2-*a*]indole-4-spiro-5'- γ -butyrolactone (13b): Bromination of 5b—1) A solution of NBS (267 mg, 1.5 mmol) in anhydrous CH₂Cl₂ (35 ml) was added to a stirred suspension of **5b** (498 mg, 1.5 mmol) in anhydrous CH₂Cl₂ (5 ml, purified by acid and base washing followed by drying over CaH₂) over a period of 7 min at room temperature. The reaction mixture was stirred for 60 min. The solution became clear and TLC showed essentially a single spot corresponding to **16b** (*R*_f 0.6, silica gel, benzene–acetone, 5 : 2). After an additional 20 min of stirring, the mixture was refluxed for 130 min until **16b** disappeared. The reaction mixture was poured into H₂O–CH₂Cl₂ (30 ml–40 ml) and the organic layer was separated. The aqueous solution was extracted with CH₂Cl₂. The CH₂Cl₂ extracts were washed with water, dried over anhydrous MgSO₄ and concentrated to leave a residue (692 mg) which was treated with ethyl acetate–hexane (1 : 1). The starting material, **5b**, was recovered as the insoluble material by filtration. The filtrate was subjected to column chromatography on silica gel (135 g, ethyl acetate–hexane, 1 : 1–5 : 1) to give crude **13b** (142 mg), which was rechromatographed on silica gel (40 g, benzene–acetone, 3 : 1) to give **13b** (97 mg, 20%) as a colorless caramel (TLC, silica gel, benzene–acetone, 3 : 1, *R*_f 0.7). Crystallization from benzene–hexane gave **13b** as colorless prisms (73 mg, 15%, mp 122–124 °C). Recrystallization from ethanol–hexane gave an analytically pure sample, mp 116–117 °C, which was used for X-ray analysis. **13b**: UV $\lambda_{\max}$ (ϵ): 244.5 (10500), 276 (1400), 285 sh (1150). IR $\nu_{\max}$: 1790 (γ -lactone), 1740, 1732, 1715 (CO). ¹H-NMR (270 MHz): 1.59 (3H, s, Me), 1.60 (3H, s, Me), 2.72 (2H, m, CH₂), 3.05 (2H, m, CH₂), 3.83 (3H, s, OMe), 5.62 (1H, s, NCHN), 7.30 (1H, dt, *J* = 7, 7 and 1 Hz, C₆–H), 7.38 (1H, d, *J* = 7 Hz, C₅–H), 7.50 (1H, dt, *J* = 8, 8 and 1 Hz, C₇–H), 7.61 (1H, d, *J* = 8 Hz, C₈–H). ¹³C-NMR (67.8 MHz): 23.81 and 24.42 (q, C₂–CH₃), 28.68 (t, CH₂CH₂), 53.15 (q, OCH₃), 65.88 (s, C-2), 82.24 (d, C-3a), 86.79 (s, C-4), 117.36 (d, C-8), 124.56 (d, C-5), 126.64 (d, C-6), 131.59 (d, C-7), 133.81 (s, C-4a), 138.82 (s, C-8a), 155.46 (s, NCO₂), 173.37, 175.70 (s, NCO, CO).²⁰ The NMR signals of the aromatic protons and the aromatic carbons were determined by the decoupling and selective decoupling methods, respectively. MS *m/z* (%): 330 (97) M⁺, 302 (39), 301 (100), 287 (13), 247 (13), 246 (67), 161 (17), 130 (10), 116 (20), 84 (10). Anal. Calcd for C₁₇H₁₈N₂O₅: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.80; H, 5.53; N, 8.44.

X-Ray analysis of **13b**: forms triclinic crystals with space group *P* $\bar{1}$ and unit cell parameters *a* = 10.926 (2) Å, *b* = 17.686 (3) Å, *c* = 9.185 (1) Å, α = 91.78 (2)°, β = 87.66 (1)°, γ = 66.09 (1)°, *V* = 1619 Å³, *Z* = 4. The intensities of 7868 reflections ($3 < 2\theta < 55^\circ$; Mo *K* α radiation) were collected, and 4795 reflections (upper limit of $\sin \theta/\lambda = 0.6181$, *F*_o > 3 σ (*F*_o)) were used for the structure analysis by the direct method²¹ using a mini computer. All the carbon, nitrogen, and oxygen atoms were located and the structure of **13b** was elucidated to be as shown in Fig. 1. The resulting *R* value at this stage was 0.101. Further refinements on a large computer²² using 5315 reflections (*F*_o > 3 σ (*F*_o)) were made with the assumption of anisotropic temperature factors for all C, N, and O atoms. Hydrogen atoms were located in difference maps and their parameters were included in the final cycles of refinement. The final *R* value was 0.059.

2) NBS (178 mg, 1 mmol) was added to a boiling solution of **5b** (332 mg, 1 mmol) in CHCl₃ (150 ml) and CF₃CO₂H (15 ml). After 1 h of refluxing, NBS (178 mg, 1 mmol) was added to the reaction mixture. The whole was refluxed for 80 min and the solvent was evaporated off. The residue was taken up with CH₂Cl₂, washed with water, and dried over MgSO₄. Evaporation of the solvent gave a residue (311 mg), which was chromatographed on silica gel to give **13b** (141 mg, 42.7%).

3) NBS (534 mg, 3 mmol) in CH₂Cl₂ (140 ml) was added to a stirred suspension of **5b** (997 mg, 3 mmol) in CH₂Cl₂ (50 ml, dried over CaCl₂ and distilled) at room temperature. The reaction mixture was stirred for 50 min and then stirred for 4.5 h at –20 to –10 °C. The solvent was evaporated off and the residue was dissolved in a small amount of benzene–acetone (4 : 1). The solution was filtered, and the filtrate was column-chromatographed on silica gel (150 g, benzene–acetone, 4 : 1) followed by rechromatography on silica gel to provide **17b** (394 mg, 29.8%), **18b** (201 mg, 19.4%), and **19b** (90 mg, 8.7%). **4a-Bromo-9a-methoxy-9-(*N*-methoxycarbonyl- α -methylalanyl)-2-oxo-2,3,4,4a,9,9a-hexahydropyrano[2,3-*b*]indole (17b)**: mp 108–109 °C (hexane–CH₂Cl₂). UV $\lambda_{\max}$ (ϵ): 238 (12500). IR $\nu_{\max}$: 3400 (NH), 1762, 1736, 1718 (CO), 1605, 1518 (amide II band). ¹H-NMR (270 MHz): 1.78 (6H, s, Me), 2.25 (2H, m, CH₂), 2.75 (2H, m, CH₂), 3.50 (3H, s, OMe), 3.60 (3H, s, CO₂Me), 5.47 (1H, s, NH, exchangeable), 7.22 (1H, dd, *J* = 7 and 1 Hz, C₆–H), 7.38 (1H, dt, *J* = 8, 8, and 1 Hz, C₇–H), 7.41 (1H, d, *J* = 7 Hz, C₅–H), 7.76 (1H, d, *J* = 8 Hz, C₈–H). ¹³C-NMR (67.8 MHz): 25.63 and 26.17 (q, C–CH₃), 30.15 (t, C-4), 34.29 (t, C-3), 51.89 (q, OCH₃), 52.20 (q, COOCH₃), 55.20 (s, C-4a), 59.49 (s, C–Me₂), 116.07 (d, C-8), 124.22 (d, C-5), 125.46 (d, C-6), 128.71 (s, C-4b), 131.01 (d, C-7), 139.10 (s, C-8a), 155.86 (s, NCO₂), 171.76, 172.88, 177.75 (s, C-2, C-10, NCO). MS *m/z* (%): 344 (2), 330 (4), 219 (53), 217 (26), 188 (39), 187 (100), 185 (53), 145 (85), 116 (70), 84 (19), 72 (21), 56 (22). Anal. Calcd for C₁₈H₂₁BrO₆N₂: C, 48.99; H, 4.80; N, 6.35. Found: C, 48.95; H, 4.77; N, 6.39. Methyl 1-(*N*-methoxycarbonyl- α -methylalanyl)-3-indolepropionate (**18b**): mp 126–127 °C (hexane–CH₂Cl₂), colorless needles. UV $\lambda_{\max}$ (ϵ): 242.5 (19000), 265 sh (8400), 273 sh (7300), 301 (7000). IR $\nu_{\max}$: 3405 (NH), 1743, 1730, 1704 (CO), 1511 (amide II band). ¹H-NMR (100 MHz): 1.70 (6H, s, Me), 2.70 (2H, t, *J* = 7 Hz, CH₂CO), 3.03 (2H, t, *J* = 7 Hz, CH₂), 3.57 (3H, s, NCO₂Me), 3.66 (3H, s, CO₂Me), 5.47 (1H, br s, NH, exchangeable), 7.18–7.60 (3H, m, arom. H), 7.75 (1H, s, C₂–H), 8.55 (1H, dd, *J* = 8 and 2 Hz, C₇–H). ¹³C-NMR (67.8 MHz): 20.33 (t, CH₂), 26.61 (q, C–CH₃), 33.66 (t, CH₂CO₂),

51.69 (q, CO_2CH_3), 52.38 (q, NCO_2CH_3), 58.60 (s, $\text{C}-\text{CH}_3$), 117.65 (d, C-7), 118.23 (d, C-4), 120.73 (s, C-3), 122.12 (d, C-2), 123.53 (d, C-5), 125.46 (d, C-6), 129.29 (s, C-3a), 137.23 (s, C-7a), 155.32 (s, NCO_2), 171.53 (s, NCO), 173.31 (s, CO_2CH_3). MS m/z (%): 346 (3) M^+ , 314 (24), 203 (100), 130 (97), 116 (38), 84 (31). Anal. Calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_5$: C, 62.41; H, 6.40; N, 8.07. Found: C, 62.08; H, 6.35; N, 7.99. 2-Methoxy-1-(*N*-methoxycarbonyl- α -methylalanyl)indolin-3-spiro-5'- γ -butyrolactone **19b**: mp 180.5–182 °C (CH_2Cl_2 –hexane), colorless needles. UV λ_{max} (ϵ): 248 (14100), 281 sh (1700), 290 (1300). IR ν_{max} : 3350 (NH), 1780 (γ -lactone), 1700, 1675, 1665 (CO), 1525 (amide II band). ^1H -NMR (270 MHz): 1.60 (3H, s, Me), 1.68 (3H, s, Me), 2.65 (1H, m) and 2.75–3.05 (3H, m) (CH_2CH_2), 2.91 (3H, s, OMe), 3.67 (3H, s, CO_2Me), 5.02 (1H, br s, NH, exchangeable), 5.30 (1H, s, CH_2Cl_2), 6.04 (1H, s, NCHO), 7.17 (1H, t, $J=8$ Hz, C_5 -H), 7.31 (1H, dd, $J=8$ and 1 Hz, C_4 -H), 7.45 (1H, dt, $J=8$, 8 and 1 Hz, C_6 -H), 8.27 (1H, d, $J=8$ Hz, C_7 -H). ^{13}C -NMR (67.8 MHz): 24.22 (t, CH_2), 26.20 (q, $\text{C}-\text{CH}_3$), 26.80 (q, $\text{C}-\text{CH}_3$), 29.43 (t, CH_2CO), 51.60 (q, OCH_3), 52.29 (q, NCO_2CH_3), 58.28 (s, $\text{C}-\text{CH}_3$), 90.13 (s, C-3), 92.52 (d, C-2), 118.52 (d, C-7), 122.32 (d, C-4), 124.79 (d, C-5), 129.08 (s, C-3a), 131.85 (d, C-6), 145.76 (s, C-7a), 155.49 (s, NHCO_2), 173.11, 174.95 (s, CO). MS m/z (%): 362 (1) M^+ , 330 (3), 219 (72), 191 (21), 158 (25), 130 (13), 116 (100), 84 (17), 72 (14). Anal. Calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_6 \cdot 1/2\text{CH}_2\text{Cl}_2$: C, 54.84; H, 5.69; N, 6.88. Found: C, 54.89; H, 5.73; N, 6.92.

4) NBS (356 mg, 2 mmol) in 5% methanol in CH_2Cl_2 (54 ml) was added to a stirred solution of **5b** (664 mg, 2 mmol) in 5% methanol in CH_2Cl_2 (70 ml) over a period of 7 min (TLC showed only one spot corresponding to **16b** when all the NBS had been added). The reaction mixture was stirred for 50 min, poured into saturated sodium bicarbonate solution and then extracted with CH_2Cl_2 . The CH_2Cl_2 extract was dried over anhydrous Na_2SO_4 and evaporated to yield a residue (682 mg), which was column-chromatographed on silica gel (50 g, ethyl acetate–hexane, 1 : 1). First elution provided **17b** (109 mg, 12.4%; R_f 0.7, SiO_2 /ethyl acetate–hexane, 1 : 1). Second elution gave **18b** (37 mg, 5.3%; R_f 0.4, the same conditions as above). The product from the third elution was rechromatographed (three times) on silica gel (25 g, ethyl acetate–hexane, 5 : 4) to give a mixture of less polar and more polar isomers of **20** (300 mg, 38%). Fourth elution gave **19b** (159 mg, 22.2%). **20a**, less polar isomer: UV λ_{max} : 250, 287 sh. IR ν_{max} : 3330 (NH, OH), 1780, 1720, 1660 (CO), 1530 (amide II band). ^1H -NMR (100 MHz): 1.60, 1.66 (s, 6H, Me), 1.80–2.30 (1H, m) and 2.30–2.70 (3H, m) (CH_2CH_2), 2.90 (3H, s, OMe), 3.57 (6H, s, CO_2Me), 4.00 (1H, br s, OH, exchangeable), 5.73 (1H, d, $J=8$ Hz, C_2 -H), 5.40–6.40 (1H, br s, NH, exchangeable), 6.92–7.20 (3H, m, arom. H), 8.11 (1H, d, $J=8$ Hz, C_7 -H). MS m/z (%): 333 (35), 273 (51), 261 (18), 219 (24), 162 (17), 160 (28), 158 (18), 146 (18), 145 (17), 132 (21), 130 (31), 116 (100), 84 (30). **20b**, more polar isomer: UV λ_{max} : 248, 277 sh, 286 sh, IR ν_{max} : 3330–3400 (NH, OH), 1730, 1660 (CO), 1520 (amide II band). ^1H -NMR (100 MHz): 1.66 (6H, s, Me), 1.80–2.50 (4H, m, CH_2CH_2), 3.35 (3H, s, OMe), 3.61 (6H, s, CO_2Me), 4.00 (1H, d, $J=8$ Hz, OH, exchangeable), 5.45 (1H, s, NH, exchangeable), 5.77 (1H, d, $J=8$ Hz, C_2 -H), 6.90–7.44 (3H, m, arom. H), 8.16 (1H, d, $J=8$ Hz, C_7 -H). MS m/z (%): 333 (1), 273 (2), 219 (100), 158 (7), 116 (21).

Both isomers were readily interconvertible in CH_2Cl_2 .

Isolation of 4a-Bromo-9-(*N*-methoxycarbonyl- α -methylalanyl)-2-oxo-2,3,4,4a,9,9a-hexahydropyrano[2,3-*b*]indole (16b**)**—NBS (18 mg, 0.1 mmol) in CH_2Cl_2 (4 ml) was added to a stirred suspension of **5b** (33 mg, 0.1 mmol) in CH_2Cl_2 at room temperature. The reaction mixture was stirred for 80 min until the solution became clear and the conversion of **5b** to **16b** was completed, then it was diluted with CH_2Cl_2 (10 ml). The CH_2Cl_2 layer was washed with water, dried over anhydrous MgSO_4 , filtered, and evaporated to give **16b**. This work-up was completed within 30 min. **16b**: UV λ_{max} : 231, 254 sh, 299.5. IR ν_{max} : 3320 (NH), 1760, 1720 sh, 1700, 1680 sh (CO), 1520 (amide II band). ^1H -NMR (100 MHz): 1.66, 1.69 (s, 6H, Me), 2.10–2.68 (2H, m, CH_2), 2.80–3.28 (2H, m, CH_2CO), 3.69 (3H, s, OMe), 5.54 (1H, s, NH), 7.01 (1H, s, NCHO), 7.06–7.55 (3H, m, arom. H), 8.20 (1H, d, $J=8$ Hz, C_8 -H).

Reaction of 13b with Trimethylsilyl Iodide (TMSI)—A solution of freshly prepared TMSI (0.1 mmol) in acetonitrile (1.2 ml) was added to a solution of **13b** (33 mg, 0.1 mmol) in anhydrous acetonitrile (1 ml) via a dry syringe under N_2 at room temperature. The reaction mixture was stirred for 75 min, poured into water (20 ml), and extracted with CH_2Cl_2 . The extract was dried over anhydrous Na_2SO_4 and concentrated. The resulting residue (41 mg) was chromatographed on silica gel (4 g, benzene–acetone, 5 : 2) to give **23** (25 mg, 77%). **23**: UV λ_{max} : 242 sh, 248, 257.5, 283, 292. IR ν_{max} : 3500–3100 (OH), 3000–2500 (COOH), 1720, 1625 (CO). ^1H -NMR (100 MHz): 1.75 (6H, s, Me), 2.68 (2H, t, $J=8$ Hz, CH_2CO), 3.26 (2H, t, $J=8$ Hz, CH_2), 3.96 (3H, s, OMe), 7.06–7.58 (3H, m, arom. H), 7.92 (1H, dd, $J=7$ and 2 Hz, C_8 -H), 8.30–9.60 (1H, br s, COOH). MS m/z (%): 330 (43) M^+ , 272 (20), 271 (100), 243 (19), 184 (11), 183 (27), 59 (10).

The reaction of **13b** (33 mg, 0.1 mmol) in DMSO (1 ml) with methanesulfonic acid (1 ml) at 1–10 °C for 7 h gave **23** (32 mg).

2,2-Dimethyl-3-(2,2,2-trichloroethoxy)carbonyl-1-oxo-2,3,4a,4-tetrahydro-1*H*-imidazo[1,2-*a*]indole-4-spiro-5'- γ -butyrolactone (13c**)**—1) NBS (178 mg, 1 mmol) was added to a boiling solution of **5c** (450 mg, 1 mmol) in CH_2Cl_2 (20 ml) containing $\text{CF}_3\text{CO}_2\text{H}$ (2 ml). After 140 min of refluxing, NBS (178 mg, 1 mmol) was added to the reaction mixture, which was further refluxed for 2 h and then concentrated. The resulting residue was treated with CH_2Cl_2 – H_2O . The CH_2Cl_2 layer was dried over anhydrous MgSO_4 , and evaporated to give a residue (577 mg), which was chromatographed on silica gel (20 g, benzene–chloroform) twice to give **13c** (129 mg, 28.8%) (TLC: $\text{SiO}_2/\text{CHCl}_3$, R_f 0.6) and **15** (TLC: $\text{SiO}_2/\text{CHCl}_3$, R_f 0.5) which was unstable and readily hydrolyzed to **9** ($\text{R}=\text{H}$). Recrystallization of **13c** from CHCl_3 –hexane gave colorless needles, mp 186–186.5 °C. UV λ_{max} (ϵ): 242.5 (10200), 275 (1300). IR ν_{max} :

1792, 1779, 1745 sh, 1735, 1720 sh (CO). $^1\text{H-NMR}$ (270 MHz): 1.70 (3H, s, Me), 1.78 (3H, s, Me), 2.75 (2H, m, CH_2), 3.05 (2H, m, CH_2), 4.84 (1H, d, $J=8$ Hz) and 4.95 (1H, d, $J=8$ Hz, CH_2CCl_3), 5.30 (1/3H, s, CH_2Cl_2), 5.65 (1H, s, NCHN), 7.32 (1H, dt, $J=8$, 8, and 1 Hz, $\text{C}_6\text{-H}$), 7.39 (1H, dd, $J=8$ and 1 Hz, $\text{C}_5\text{-H}$), 7.50 (1H, dt, $J=8$, 8, and 1 Hz, $\text{C}_7\text{-H}$), 7.63 (1H, dd, $J=8$ and 1 Hz, $\text{C}_8\text{-H}$). $^{13}\text{C-NMR}$ (67.8 MHz): 23.87 (q, C-CH_3), 24.73 (q, C-CH_3), 28.56, 28.77 (t, CH_2CH_2), 66.46 (s, C-CH_3), 75.30 (t, OCH_2), 82.32 (d, C-3a), 86.61 (s, C-4), 94.62 (s, CCl_3), 117.42 (d, C-8), 124.53 (d, C-5), 126.81 (d, C-6), 131.70 (d, C-7), 133.63 (s, C-4a), 138.70 (s, C-8a), 153.16 (s, NCO_2), 173.02, 175.38 (s, NCO , CO). MS m/z (%): 448 (64) $\text{M}^+ + 2$, 446 (56) M^+ , 421 (35), 419 (79), 417 (100) $\text{M}^+ - \text{CHO}$, 366 (45), 364 (66), 362 (89), 243 (40), 204 (43), 188 (55), 160 (41), 149 (45), 131 (41), 84 (57). Exact mass calcd for $\text{C}_{18}\text{H}_{17}\text{Cl}_3\text{N}_2\text{O}_5$: $\text{M}^+ = 446.0205$, Found 446.0209; $\text{M}^+ + 2 = 448.0175$, Found 448.0170; $\text{M}^+ + 4 = 450.0145$, Found 450.0146. Anal. Calcd for $\text{C}_{18}\text{H}_{17}\text{Cl}_3\text{N}_2\text{O}_5 \cdot 1/6\text{CH}_2\text{Cl}_2$: C, 47.24; H, 4.05; N, 6.07. Found C, 47.19; H, 3.80; N, 6.00.

2) NIS (45 mg, 0.2 mmol) in acetonitrile (3 ml) was added to a stirred solution of **5c** (91 mg, 0.2 mmol) in acetonitrile (2 ml). The reaction mixture was stirred for 5 h at room temperature and for 3.5 h at reflux. Work-up gave **13c** (4 mg, 4%) and recovered **5c** (64 mg, 70%).

2,2-Dimethyl-1-oxo-2,3,3a,4-tetrahydro-1H-imidazo[1,2-a]indole-4-spiro-5'- γ -butyrolactone (2)—A solution of **13c** (45 mg, 0.1 mmol) in AcOH (2 ml) was treated with Zn (45 mg). The reaction mixture was stirred for 1 h, then further Zn (45 mg) was added and the reaction was continued for 1 h at room temperature. The insoluble material was filtered off. The filtrate was concentrated *in vacuo*. The resulting residue was chromatographed on silica gel (3 g, CHCl_3 -acetone, 20:1) to give **2** (22 mg, 80%). Recrystallization from CHCl_3 -hexane gave colorless needles, mp 216–217.5 °C. UV λ_{max} (ϵ): 246.5 (11800), 284 sh (1500). IR ν_{max} : 3350 (NH), 1783 (γ -lactone), 1711 (CO), 1610 (PhNCN). $^1\text{H-NMR}$ (270 MHz): 1.43 (3H, s, Me), 1.49 (3H, s, Me), 2.45 (1H, br s, NH, exchangeable), 2.53 (1H, ddd, $J=14$, 14, and 9 Hz) and 2.73–2.97 (3H, m, CH_2CH_2), 5.24 (1H, s, NCHN), 7.21 (1H, t, $J=7.5$ Hz, $\text{C}_6\text{-H}$), 7.39 (1H, d, $J=7.5$ Hz, $\text{C}_5\text{-H}$), 7.47 (1H, t, $J=8$ Hz, $\text{C}_7\text{-H}$), 7.59 (1H, d, $J=8$ Hz, $\text{C}_8\text{-H}$). $^{13}\text{C-NMR}$ (67.8 MHz): 24.39 (q, C-CH_3), 24.88 (q, C-CH_3), 28.85, 30.32 (t, CH_2CH_2), 66.46 (s, C-CH_3), 81.66 (d, C-3a), 85.95 (s, C-4), 115.84 (d, C-8), 124.51 (d, C-5), 125.37 (d, C-6), 131.93 (d, C-7), 132.11 (s, C-4a), 138.96 (s, C-8a), 174.46, 175.73 (s, NCO , CO). MS m/z (%): 272 (67) M^+ , 244 (35), 243 (77), 201 (16), 189 (22), 188 (100), 161 (27), 160 (35), 131 (20), 130 (20), 104 (52), 58 (67), 42 (28). Exact mass calcd for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_3$: 272.1162. Found 272.1161. Anal. Calcd for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_3 \cdot 1/3\text{H}_2\text{O}$: C, 64.73; H, 6.04; N, 10.07. Found: C, 65.01; H, 5.82; N, 10.03.

Formation of 13b from 2—A mixture of **2** (6 mg, 0.02 mmol), anhydrous K_2CO_3 (8 mg, 0.06 mmol), and methyl chloroformate (7.56 mg, 0.08 mmol) in acetone (2 ml) was refluxed for 1 h then further methyl chloroformate (7.56 mg) in acetone (1 ml) was added. After 2 h of refluxing, additional methyl chloroformate (7.56 mg) in acetone (1 ml) and anhydrous K_2CO_3 (8 mg) were added to the reaction mixture. The whole was refluxed for 2.5 h and then evaporated. The residue was taken up with CH_2Cl_2 . The CH_2Cl_2 extract was filtered, dried over anhydrous MgSO_4 and evaporated. Purification of the crude product by column chromatography on silica gel (3 g, CHCl_3 -acetone, 40:1) gave **13b** (6 mg) which was identical with that obtained by bromination of **5b**, both spectroscopically ($^1\text{H-NMR}$ and IR, UV) and in TLC behavior.

Acknowledgement We thank Miss N. Takahashi for the preexperimental work for this research. We also acknowledge financial support of this research by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan. We are grateful to Mrs. H. Seki, Misses S. Nakajima and R. Hara, and Mr. T. Kuramochi of the Analytical Center of our University for spectral measurements (MS and NMR) and microanalysis.

References and Notes

- 1) A part of this work has been published as a communication. M. Nakagawa, M. Taniguchi, M. Sodeoka, M. Ito, K. Yamaguchi, and T. Hino, *J. Am. Chem. Soc.*, **105**, 3709 (1983).
- 2) a) J. Clardy, J. P. Springer, G. Büchi, K. Matsuo, and R. Wightman, *J. Am. Chem. Soc.*, **97**, 663 (1975); b) G. Büchi, K. C. Luk, B. Koffe, and J. M. Townsend, *J. Org. Chem.*, **42**, 244 (1977); c) J. P. Springer, *Tetrahedron Lett.*, **1979**, 339.
- 3) a) M. Yamazaki, H. Fujimoto, and E. Okuyama, *Tetrahedron Lett.*, **1976**, 2861; b) *Idem*, *Chem. Pharm. Bull.*, **25**, 2554 (1977); c) *Idem*, *ibid.*, **26**, 111 (1978); d) M. Yamazaki, E. Okuyama, and Y. Maebayashi, *ibid.*, **27**, 1611 (1979).
- 4) G. Büchi, P. R. DeShong, S. Katsumura, and Y. Sugimura, *J. Am. Chem. Soc.*, **101**, 5084 (1979).
- 5) T. Ohnuma, Y. Kimura, and Y. Ban, *Tetrahedron Lett.*, **22**, 4969 (1981).
- 6) a) W. B. Lawson, A. Patchornik, and B. Witkop, *J. Am. Chem. Soc.*, **82**, 5918 (1960); W. B. Lawson and B. Witkop, *J. Org. Chem.*, **26**, 263 (1961); b) R. L. Hinman and C. P. Bauman, *ibid.*, **29**, 1206, 2431 (1964); c) R. J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, 1970, p. 14; d) W. J. Houlihan (ed.), "Indoles," Part 2, Wiley-Interscience, New York, 1972, p. 127.
- 7) a) T. Hino, M. Nakagawa, T. Wakatsuki, K. Ogawa, and S. Yamada, *Tetrahedron*, **23**, 1441 (1967); b) T. Hino, M. Nakagawa, and S. Akaboshi, *Chem. Pharm. Bull.*, **15**, 1800 (1967).

- 8) T. Kobayashi and N. Inokuchi, *Tetrahedron*, **20**, 2055 (1964).
- 9) T. Hino, T. Nakamura, and M. Nakagawa, *Chem. Pharm. Bull.*, **23**, 2990 (1975).
- 10) a) T. Hino, H. Miura, T. Nakamura, R. Murata, and M. Nakagawa, *Heterocycles*, **3**, 895 (1975); b) T. Hino, H. Miura, R. Murata, and M. Nakagawa, *Chem. Pharm. Bull.*, **26**, 3695 (1978).
- 11) D. A. Neklyudov, L. A. Shchukina, and N. N. Suvorov, *Zh. Obshch. Khim.*, **37**, 797 (1967); cf, *idem*, *Chem. Abstr.* **68**, 30024g (1968).
- 12) V. O. Illi, *Synthesis*, **1979**, 387.
- 13) A. Shaffie and S. Sattari, *Synthesis*, **1981**, 389.
- 14) J. F. Klebe, H. Finkbeiner, and D. M. White, *J. Am. Chem. Soc.*, **88**, 3390 (1966).
- 15) Y. Klausner and M. Chorev, *J. Chem. Soc., Perkin Trans. 1*, **1977**, 627.
- 16) I. Saito, T. Matsuura, M. Nakagawa, and T. Hino, *Acc. Chem. Res.*, **10**, 346 (1977), and references cited therein.
- 17) J. R. Long, *Aldrichimica Acta*, **14**, 63 (1981).
- 18) a) M. E. Jung and M. A. Lyster, *Chem. Commun.*, **1978**, 315; b) R. S. Lott, V. S. Chauhan, and C. H. Stammer, *ibid.*, **1979**, 495, c) H. Schmidt, *Aldrichimica Acta*, **14**, 31 (1981).
- 19) H. Irie, H. Nakanishi, N. Fujii, Y. Mizuno, T. Fushimi, S. Funakoshi, and H. Yajima, *Chem. Lett.*, **1980**, 705.
- 20) R. Goutarel, M. Pais, H. E. Gottlieb, and E. Wenkert, *Tetrahedron Lett.*, **1978**, 1235.
- 21) P. Main, M. M. Woolfson, L. Lessinger, G. Germain, Declerq, MULTAN 74; A System of Computer Programs for the Automatic Solution of Crystal Structure from X-Ray Diffraction Data, University of York, England and Louvain-la-neuve, Belgium, 1974; The ORTEP drawings: C. K. Johnson, ORTEP, Report ORNL-3794, Oak Ridge National Lab., Tennessee, 1965.
- 22) HITAC M-280H/M-200H system (VOS3/JSS4), Computer Center, University of Tokyo. Program: J. M. Stewart, G. J. Kruger, H. L. Ammon, H. L. Dickinson, and S. R. Hall, the X-Ray System-version of June 1972, Tech. Rep. TR-192, Computer Science Center, University of Maryland, College Park, Maryland.