Pergamon

Tetrahedron, Vol. 52, No. 24, pp. 8169-8180, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00386-9

Construction of Three Types of Fused Isoindoles *via* Furan-Pyrrole Ring Exchange Reaction

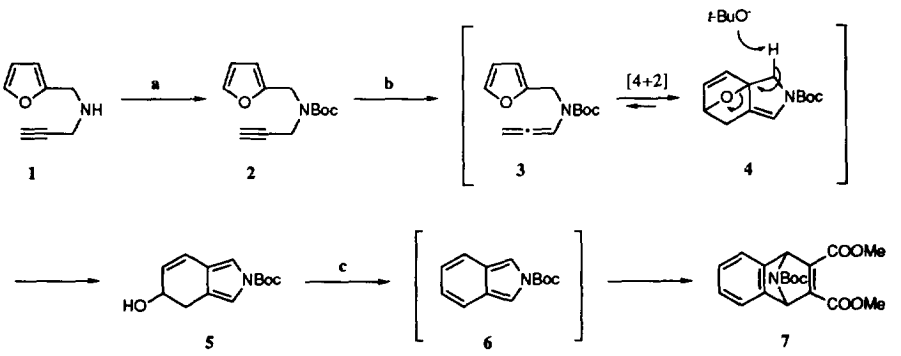
Mase Lee, Hiroyuki Moritomo, and Ken Kanematsu*

Institute of Synthetic Organic Chemistry, Faculty of Pharmaceutical Sciences, Kyushu University 62, Maidashi, Higashiku, Fukuoka 812-82, Japan

Abstract: The new synthetic route of three types of fused isoindoles using furan-pyrrole ring exchange reaction as the main synthetic strategy is presented. Benzoisoindoles **1 7**, **2 8** and **3 8** were synthesised from bicyclic furans **1 4**, **2 5** and **3 5** respectively, which were trapped with dimethyl acetylenedicarboxylate. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Isoindole chemistry is a rather new field within heterocyclic chemistry partly because isoindoles are both rare in nature and very unstable. A few synthetic approaches[1] have been examined for academic interest and in anticipation of the future biological estimation of corresponding indole compounds. Recently, interesting biological activities, including alpha 2A-adrenoceptor antagonist activity[2a] and antimicrobial activity[2b] of isoindole related compounds have been reported. Practically, isoindole syntheses are restricted by the limited stability of ring systems. In spite of having considerable aromaticity, isoindoles are unstable due to their high kinetic reactivity and this fact has restricted methods to construct isoindoles.

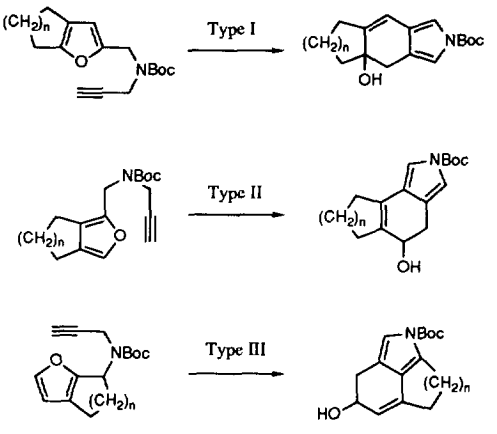


Scheme 1. ***Reagents and Conditions*** (a) di-*t*-butyl dicarbonate, DMAP(cat.), NEt_3, CH_2Cl_2, r.t., 92% (b) *t*-BuOK (5 eq.), *t*-BuOH, 40 ℃, 63% (c) PPTS (cat.), $CH(OCH_3)_3$, DMAD, THF, reflux, 80%

Previously, we developed a new route to the isoindole nucleus *via* furan-pyrrole ring exchange reaction.[3] As an extension of the furan ring transfer reaction,[4] *N*-Boc furfurylpropargylamine **2** was treated with *t*-BuOK in *t*-BuOH at 40 °C to afford [3,4] fused pyrrole compound **5** *via* the tandem reaction of intramolecular Diels-Alder reaction and subsequent base-catalyzed epoxide opening of the resulting adduct **4**. Dehydration of compound **5** with a weak acid and methyl orthoformate as the water binding reagent generated the isoindole **6**. Although compound **6** itself could not be isolated because isoindoles are very unstable species, compound **6** was trapped successfully with dimethyl acetylenedicarboxylate *in situ* (Scheme 1).

In connection with this methodology, we now describe the construction of tricyclic isoindoles in detail. In this field, few examples[5] were reported until now that these types of polycyclic isoindoles were produced.

We classified tricyclic isoindoles into three types based on their condensing patterns as shown in Scheme 2.



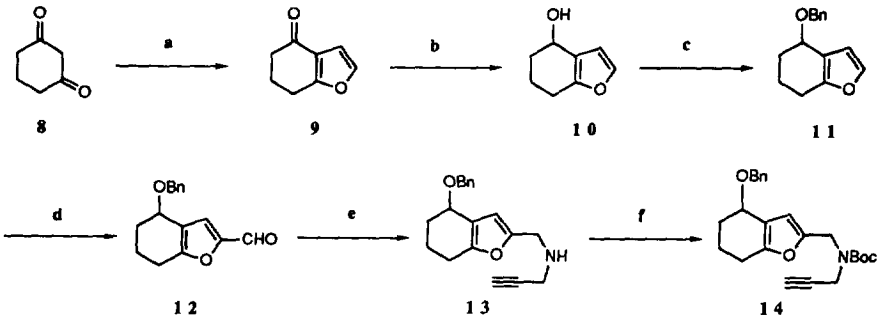
Scheme 2.

RESULTS AND DISCUSSION

At first, Type I reaction was examined. The synthesis of substrate **14** was carrried out as shown in Scheme 3.

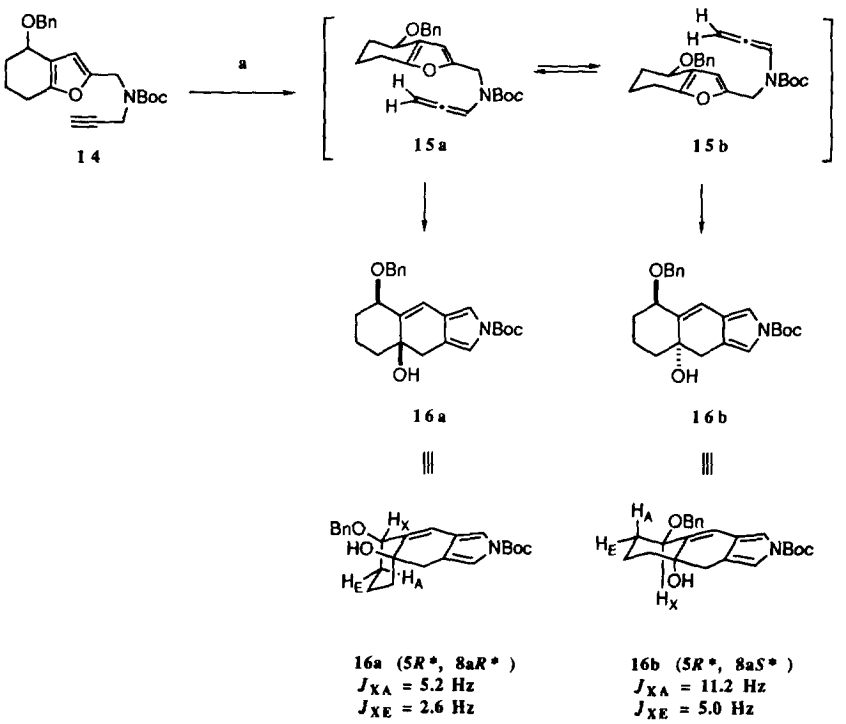
Bicyclic furan **9** was prepared from 1, 3-cyclohexanedione **8** by modified Feist-Beniary furan synthesis with chloroacetaldehyde[6] in 79% yield. Then the carbonyl group was reduced with $NaBH_4$ and the resulting hydroxyl group was protected as benzyl ether, with the intention of elevating the boiling point to provide convenience of handling and confering stability against acidic and basic conditions. Formylation of compound **11** according to Vilsmeier-Haack protocol[7] followed by reductive amination with propargylamine and $NaBH_3CN$ afforded secondary amine **13**.

Based on the good result obtained from the reaction of Scheme 1 using the Boc group as the third protective group of the reaction substrate amine **2**, compound **13** was protected with Boc_2O. This protection under the same conditions used in the Scheme 1 did not occur at all. However, addition of a stoichiometric amount of hydroxylamine dramatically changed both the reaction speed and the yield.[8]



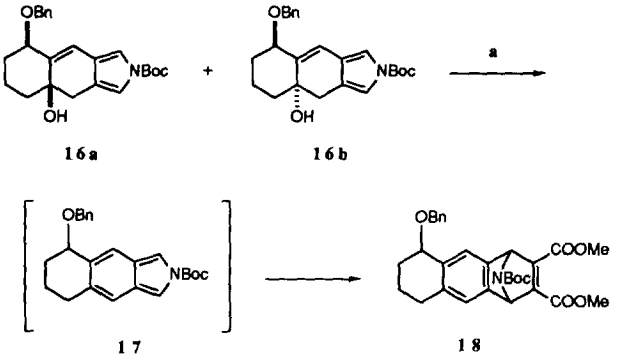
Scheme 3. ***Reagents and Conditions*** (a) $ClCH_2CHO$, $NaHCO_3$ *aq.*, then H_2SO_4 *aq.*, 75% (b) $NaBH_4$, EtOH, r.t., 89% (c) NaH, BnBr, DME, r.t., quant. (d) $POCl_3$, DMF, r.t., 83% (e) propargylamine, $NaBH_3CN$, MeOH, r.t., 72% (f) di-*t*-butyl dicarbonate, NH_2OH•HCl, NEt_3, CH_2Cl_2, r.t., 99%.

Furan-Pyrrole Ring Exchange Reaction proceeded with *t*-BuOK under refluxing conditions in *t*-BuOH in high yield and two diastereomers, **16a** and **16b**, were obtained in the ratio of 1:3. This reaction needed a higher temperature than that of original reaction. The relative configuration of these two isomers was characterized by inspection of the vicinal coupling constants of H_A, H_E and H_X protons on the ^1H NMR spectra (Scheme 4).



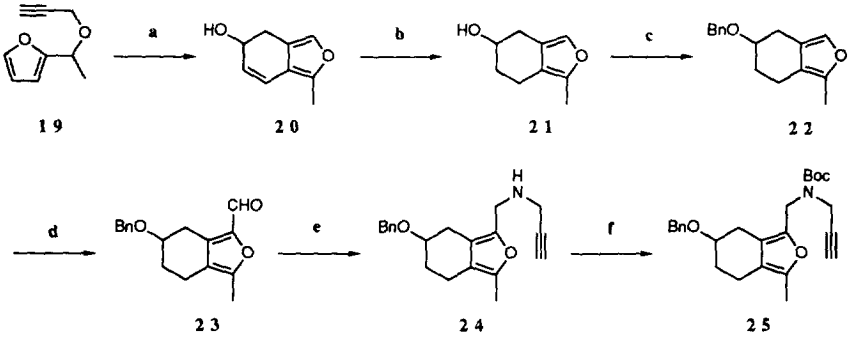
Scheme 4. ***Reagents and Conditions*** (a) *t*-BuOK, *t*-BuOH, reflux, 88%

Obtained reaction products **16a** and **16b** were dehydrated with PPTS and methyl orthoformate, and the generated benzo[*f*]isoindole **17** thus generated was trapped with dimethyl acetylenedicarboxylate *in situ*.



Scheme 5. ***Reagents and Conditions*** (a) PPTS (cat.), $CH(OCH_3)_3$, DMAD, CH_2Cl_2, reflux, 55%

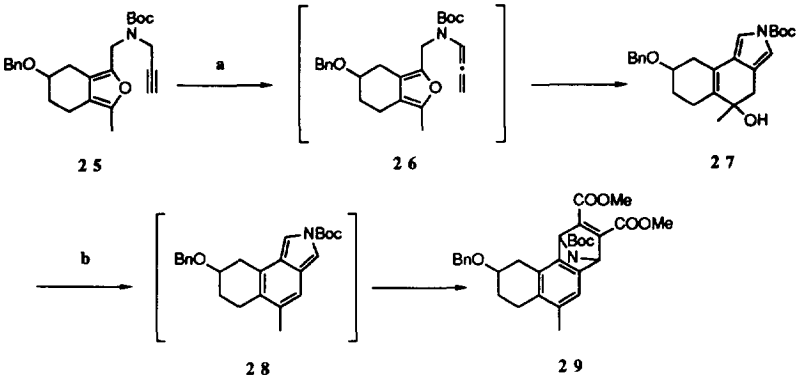
Next, we examined Type II reaction. Bicyclic furan **20** was chosen as the starting material, which was reported during the course of investigating furan ring transfer reaction in our laboratory.[4a] The double bond of this isobenzofuran **20** was reduced by catalytic hydrogenation to give a hydroxyl compound, which was protected in the form of benzyl ether for the same reason as in the case of Type I reaction. A similar strategy adopted in synthesizing the Type I substrate was used to introduce propargyl moiety. The reaction conditions were almost the same as those of Type I reaction.



Scheme 6. ***Reagents and Conditions*** (a) *t*-BuOK (20 eq.), *t*-BuOH, 70 ℃ (b) 5% Pd-C, H_2, MeOH, r.t., 48% (from **20**) (c) NaH, BnBr, DMF, r.t., quant. (d) $POCl_3$, DMF, r.t., 85% (e) propargylamine, $NaBH_3CN$, MeOH, r.t., 59% (f) di-*t*-butyl dicarbonate, NH_2OH•HCl, NEt_3, CH_2Cl_2, r.t., quant.

Furan-pyrrole ring exchange reaction proceeded at a lower temperature than that of the Type I reaction, although the yield was somewhat lower, with purification of the product resulting in a further lowering of the yield. Column chromatography on silica gel over a long period of time led to decomposition and coloration of the product **27**. Thus, the crude product which had passed through a short column was used directly for the

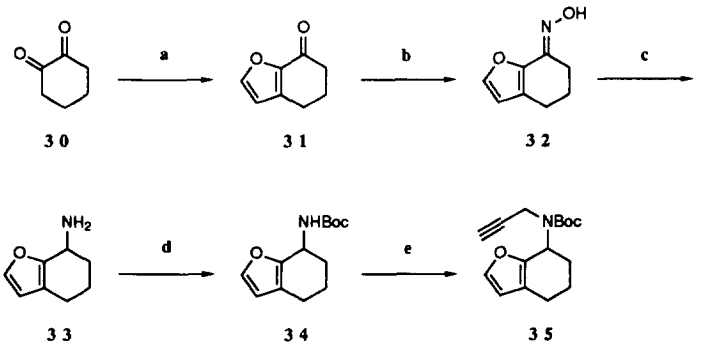
following reaction. Dehydration and trapping of generated benzo[*e*]isoindole **28** were also performed successfully.



Scheme 7. Reagents and Conditions (a) *t*-BuOK (5 eq.), *t*-BuOH, 40 ℃, 50% (b) PPTS (cat.), $CH(OCH_3)_3$, DMAD, CH_2Cl_2, reflux, 72%

Finally, Type III reaction was examined. Bicyclic furan **31** was readily obtained following to modified Feist-Beniary furan synthesis of 1,2-cyclohexanedione **30**. However, condensation of compound **31** with propargylamine was difficult. The reaction did not proceed at all under the same conditions used in synthesizing the corresponding substrates of Types I and II reaction. A stoichiometric amount of cerium (III) chloride was added to elevate the reactivity of carbonyl group but this proved to be in vain.

Thus, the introduction of another nitrogen nucleophile was attempted. The reaction with more nucleophilic hydroxylamine afforded oxime **32**. However, no reduction of this resulting oxime **32** to amine **33** occurred (catalytic hydrogenation, borane reduction, Beauvault-Blanc reduction).

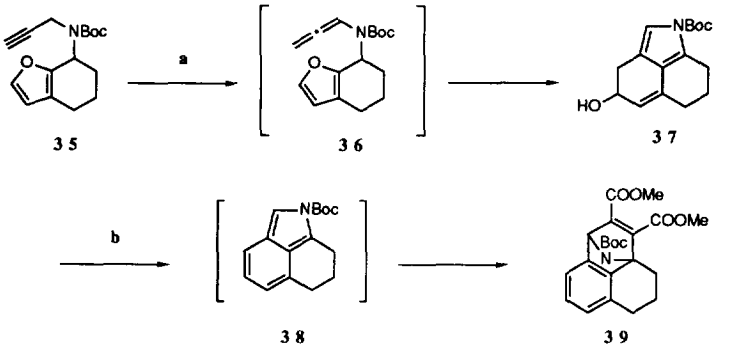


Scheme 8. *Reagents and Conditions* (a) $ClCH_2CHO$, $NaHCO_3$ *aq.*, then H_2SO_4 *aq.*, 65% (b) NH_2OH•HCl, $NaHCO_3$, MeOH, reflux, 66% (c) $LiAlH_4$, THF, 40 ℃ (d) di-*t*-butyl dicarbonate, NEt_3, CH_2Cl_2, r.t., 98% (from **32**) (e) propargyl bromide, NaH, DMF, r.t., 79%

Finally, the reduction was accomplished with lithium aluminum hydride in tetrahydrofuran. Although previous attempts to produce the same reduction with lithium aluminum hydride had been unsuccessful, the reaction proceeded simply by changing the solvent from ether to tetrahydrofuran. The structure was characterized by the ^1H NMR spectrum of the crude product, however, further purification by column chromatography on silica gel resulted in decomposition. This crude amine **33** was then used in further reaction after only filtration and removal of the solvent.

Protection with Boc group was accomplished under usual conditions and the propargyl group was introduced with propargyl bromide to afford the substrate **35**. Attempts to introduce the propargyl group prior to the Boc protection resulted in a dipropargyl product.

Reaction using *t*-BuOK in *t*-BuOH proceeded smoothly at 40 °C in 1 hr to give the desired product **37**. Dehydration using PPTS and methyl orthoformate followed by treatment of dimethyl acetylenedicarboxylate were carried out successfully to give the product **39**.



Scheme 9. ***Reagents and Conditions*** (a) *t*-BuOK (5 eq.), *t*-BuOH, 40 °C, 66% (b) PPTS (cat.), $CH(OCH_3)_3$, DMAD, THF, r.t., 86%

EXPERIMENTAL SECTION

General Melting points were determined on Yanaco micro melting point apparatus without correction. ^1H-NMR spectra were taken on JEOL GX-270 (270 MHz) spectrometer. ^{13}C-NMR spectra were recorded on JEOL GX-270 (67.8 MHz). Chemical shifts are reported in δ units (part per million downfield from Me_4Si). IR spectra were determined on JASCO IR A-100 infrared spectrophotometer. Mass spectra (MS) were determined on JEOL D-300 or JEOL DX-300. Analytical thin-layer chromatographies (TLC) were performed with E. M. Merck precoated TLC plates (Kieselgel 60 F_{254}, 0.2 mm). Chromatography separations were carried out on E. M. Merck Kieselgel 60 (70-230 mesh) as the stationary phase. All solvents were purified and dried prior to use according to standard procedures. All reactions sensitive to moisture or air were performed under argon. Reaction vessels were flame-dried or oven-dried and allowed to cool under inert atmosphere for moisture-sensitive reactions.

4-Hydroxy-4,5,6,7-tetrahydrobenzofuran 10 A solution of **9** (2.05 g, 15.1 mmol) in methanol (40 mL) was treated with sodium borohydride (1.14 g, 30.1 mmol) at 0 °C. The reaction mixture was stirred at r.t. for 2 h. The solvent was removed in vacuo. Water was added to the residue and the resulting mixture was extracted with ether. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography [hexane-ethyl acetate (2:1)] afforded **10** (1.86 g, 89%) as a colorless oil. IR ν_{max} (neat) cm^{-1} 3350, 2950, 2860; ^{1}H-NMR ($CDCl_3$) δ 7.27-7.26 (1 H, m), 6.40 (1 H, d, J = 2.0 Hz), 4.74-4.72 (1 H, m), 2.70-2.47 (2 H, m), 2.60-1.75 (4 H, m), 1.73 (1 H, bs) ; EIMS m/z 138 (M^+).

4-Benzyloxy-4,5,6,7-tetrahydrobenzofuran 11 A solution of **10** (1.76 g, 12.7 mmol) in dry dimethoxymethane (20 mL) was treated with sodium hydride (60%, 1.02 g, 25.5 mmol) under argon. The resulting mixture was stirred at 0 °C for 1 h. Benzyl bromide (2.27 mL, 19.1 mmol) was added dropwise to the reaction mixture and the resulting mixture was stirred at r.t. for 4 h under argon. Saturated ammonium chloride solution was added and extracted with methylene chloride. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography [hexane-ethyl acetate (25:1)] afforded **11** (2.91 g, quant.) as a colorless oil. IR ν_{max} (neat) cm^{-1} 2940, 2850; ^{1}H-NMR ($CDCl_3$) δ 7.41-7.26 (6 H, m), 6.35 (1 H, d, J = 2.0 Hz), 4.65 (1 H, d, J = 11.9 Hz), 4.47 (1 H, t, J = 3.8 Hz), 2.72-2.47 (2 H, m), 2.15-1.95 (2 H, m), 1.87-1.73 (2 H, m); FABMS m/z 228 (M^+); HR FABMS calcd for $C_{15}H_{16}O_2$ 228.1150, found 228.1153.

2-(4-Benzyloxy-4,5,6,7-tetrahydro)benzofuraldehyde 12 A solution of **11** (1.10 g, 4.82 mmol) in dry dimethyl formamide (6 mL) was treated with Vilsmeier reagent (prepared from 3 mL of dimethyl formamide and 2 mL of phosphorous oxychloride, 1.5 mL) under argon. The resulting mixture was stirred at r.t. for 30 min. The reaction mixture was quenched with 10% sodium hydroxide solution. Saturated sodium bicarbonate solution was added and the mixture was extracted with methylene chloride. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography [hexane-ethyl acetate (4:1)] afforded **12** (1.02 g, 83%) as a yellow oil. IR ν max (neat) cm^{-1} 2950, 2860, 1670; ^{1}H-NMR ($CDCl_3$) δ 9.52 (1 H, s), 7.42-7.28 (5 H, m), 7.18 (1 H, s), 4.67 (1 H, d, J = 11.9 Hz), 4.60 (1 H, d, J = 11.9 Hz), 4.50 (1 H, t, J = 4.5 Hz), 2.78 (1 H, dt, J = 5.6, 18.1 Hz), 2.69-2.57 (1 H, m), 2.20-1.96 (2 H, m), 1.92-1.80 (2 H, m), 1.65 (1 H, brs); FABMS m/z 257 ($M+H^+$); HR FABMS calcd for $C_{16}H_{17}O_3$ ($M+H^+$) 257.1177, found 257.1174.

***N*-Propargyl-2-(4-benzyloxy-4,5,6,7-tetrahydro)benzofurfurylamine 13** A solution of **12** (633 mg, 2.47 mmol) in dry methanol (10 mL) was treated with propargylamine (0.85 mL, 12.4 mmol) and sodium cyanoborohydride (777 mg, 12.4 mmol) under argon. The reaction mixture was stirred at r.t. overnight. The solvent was removed in vacuo. Water was added to the residue and the mixture was extracted with ether. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography [hexane-ethyl acetate (2:1)] afforded **13** (526 mg, 72%) as a yellow oil. IR ν_{max} (neat) cm^{-1} 3300, 2940, 2850, 2100; ^{1}H-NMR ($CDCl_3$) δ 7.40-7.24 (5 H, m), 6.19 (1 H, s), 4.64 (1 H, d, J = 12.2 Hz), 4.59 (1 H, d, J = 12.2 Hz), 4.43 (1 H, t, J = 4.5 Hz), 3.82 (2 H, s), 3.44 (2 H, d, J = 2.3 Hz), 2.65 (1 H, dt, J = 5.1, 16.5 Hz), 2.56-2.45 (1 H, m), 2.24 (1 H, t, J = 2.3 Hz), 2.11-1.94 (2 H,

m), 1.85-1.72 (2 H, m), 1.60 (1 H, brs); FABMS *m/z* 294 ($M-H^+$); HR FABMS calcd for $C_{19}H_{20}O_2N$ ($M-H^+$) 294.1493, found 294.1494.

***N*-*t*-Butoxycarbonyl-*N*-propargyl-2-(4-benzyloxy-4,5,6,7-tetrahydro)benzofurfurylamine 14** A solution of **13** (1.49 g, 5.06 mmol) in dry methylene chloride (15 mL) was treated with triethylamine (7.05 mL, 50.6 mmol) and hydroxylamine hydrochloride (352 mg, 5.06 mmol). Di-*t*-butyl dicarbonate (1.40 mL, 6.07 mmol) was added dropwise to the reaction mixture and the resulting mixture was stirred at r.t. for 1.5 h under argon. Saturated ammonium chloride solution was added to the resulting mixture and the mixture was extracted with methylene chloride. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography [hexane-ethyl acetate (8:1)] afforded **14** (1.99 g, 99%) as a colorless oil. IR ν_{max} (neat) cm^{-1} 3290, 2970, 2930, 2850, 2100, 1690; ^{1}H-NMR ($CDCl_3$) δ 7.40-7.25 (5 H, m), 6.20 (1 H, brs), 4.64 (1 H, d, J = 11.9 Hz), 4.58 (1 H, d, J = 11.9 Hz), 4.45 (2 H, brs), 4.42 (1 H, t, J = 3.3 Hz), 4.05 (2 H, brs), 2.63 (1 H, dt, J = 5.1, 16.5 Hz), 2.55-2.43 (1 H, m), 2.20 (1 H, t, J = 2.3 Hz), 2.10-1.94 (2 H, m), 1.85-1.69 (2 H, m), 1.49 (9 H, s); FABMS *m/z* 395 (M^+); HR FABMS calcd for $C_{24}H_{29}O_4N$ (M^+) 395.2096, found 395.2096.

(5*R,8a*R**)-*N*-*t*-Butoxycarbonyl-5-benzyloxy-8a-hydroxy-5,6,7,8,8a,9-hexahydrobenzo[*f*]-isoindole 16a and (5*R**,8a*S**)-*N*-*t*-Butoxycarbonyl-5-benzyloxy-8a-hydroxy-5,6,7,8,8a,9-hexahydrobenzo[*f*] isoindole 16b** A solution of potassium *t*-butoxide (364 mg, 3.24 mmol) in *t*-butanol (3 mL) was refluxed for 30 min under argon. The resulting solution was cooled to 40 °C and a solution of **14** (256 mg, 0.65 mmol) in *t*-butanol (3 mL) was added dropwise. The reaction mixture was refluxed for 10 min under argon. Saturated ammonium chloride solution was added to the resulting mixture and the mixture was extracted with ether. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography [hexane-ethyl acetate (8:1)] afforded **16** (227 mg, 88%; **16a** 56.8 mg, **16b** 170 mg). **16a**: as a colorless solid. IR ν_{max} ($CHCl_3$) cm^{-1} 3450, 2950, 2910, 2840, 1715; ^{1}H-NMR ($CDCl_3$) δ 7.36-7.24 (5 H, m), 7.15 (1 H, d, J = 1.7 Hz), 7.00 (1 H, brs), 6.35 (1 H, s), 4.59 (1 H, d, J = 12.0 Hz), 4.39 (1 H, d, J = 12.0 Hz), 4.05 (1 H, dd, J = 5.2, 2.6 Hz), 3.59 (1 H, d, J = 1.3 Hz), 2.96 (1 H, d, J = 16.8 Hz), 2.64 (1 H, dt, J = 1.7, 16.8 Hz), 2.18-2.03 (4 H, m), 1.65-1.64 (2 H, m), 1.57 (9 H, s); FABMS *m/z* 395 (M^+); HR FABMS calcd for $C_{24}H_{29}O_4N$ (M^+) 395.2096, found 395.2099. **16b**: a colorless oil. IR ν_{max} (neat) cm^{-1} 3450, 2950, 2870, 1735; ^{1}H-NMR ($CDCl_3$) δ 7.42-7.26 (5 H, m), 7.06 (1 H, s), 6.98 (1 H, s), 6.68-6.67 (1 H, m), 4.70 (1 H, d, J = 12.0 Hz), 4.64 (1 H, d, J = 12.0 Hz), 4.29 (1 H, ddd, J = 2.0, 5.0, 11.2 Hz), 2.90 (1 H, d, J = 16.5 Hz), 2.74 (1 H, dd, J = 1.7, 16.5 Hz), 2.29-2.23 (1 H, m), 1.97-1.92 (1 H, m), 1.84-1.77 (1 H, m), 1.81 (1 H, brs, D_2O exchangeable), 1.75-1.68 (1 H, m), 1.66-1.51 (1 H, m), 1.57 (9 H, s), 1.39 (1 H, ddd, J = 4.3, 11.9, 23.4 Hz); FABMS *m/z* 395 (M^+); HR FABMS calcd for $C_{24}H_{29}O_4N$ (M^+) 395.2096, found 395.2099.

***N*-*t*-Butoxycarbonyl-6-benzyloxy-2,3-dimethoxycarbonyl-1,4,6,7,8,9-hexahydro-1,4-imino-anthracene 18** A solution of **16** (103 mg, 0.26 mmol) in dry methylene chloride (2 mL) was treated with dimethyl acetylenedicarboxylate (0.039 mL, 0.31 mmol) and methyl orthoformate (0.29 mL, 2.62 mmol) in the presence of a catalytic amount of pyridinium *p*-toluenesulfonic acid under argon. The resulting mixture was

stirred at r.t. for 40 min. Saturated sodium bicarbonate solution was added to the residue and the mixture was extracted with methylene chloride. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography [hexane-ethyl acetate (4:1)] afforded **18** (74.6 mg, 55%) as a colorless oil. IR ν_{max} (neat) cm^{-1} 2980, 2950, 2860, 1715; ^{1}H-NMR ($CDCl_3$) δ 7.41-7.27 (6 H, m), 7.14 (1 H, brs), 5.73 (1 H, brs), 5.69 (1 H, brs), 4.68 (1 H, dd, J = 5.3, 11.9 Hz), 4.57 (1 H, dd, J = 3.3, 11.9 Hz), 4.46 (1 H, brs), 3.79 (3 H, s), 3.78 (3 H, d, J = 3.0 Hz), 2.85-2.59 (2 H, m), 2.10-1.85 (3 H, m), 1.77-1.68 (1 H, m), 1.39 (9 H, d, J = 2.3 Hz); FABMS *m/z* 520 ($M+H^+$); HR FABMS calcd for $C_{30}H_{34}O_7N$ ($M+H^+$) 520.2335, found 520.2332.

5-Hydroxy-1-methyl-4,5,6,7-tetrahydroisobenzofuran 21 A solution of crude **20** in methanol (240 mL) was treated 5% palladium on carbon (80 mg). The reaction mixture was stirred at r.t. for 20 hr under hydrogen. The catalyst was removed by filtration and washed with ether. The solvent was removed in vacuo. Purification of the residue by column chromatography [hexane-ethyl acetate (2:1)] afforded **21** (243 mg, 48%) as a colorless oil. IR ν_{max} (neat) cm^{-1} 3330, 2900, 2830; ^{1}H-NMR ($CDCl_3$) δ 7.04 (1 H, s), 4.13-4.05 (1 H, m), 2.85 (1 H, dd, J = 4.9, 15.5 Hz), 2.62 (1 H, dt, J = 6.3, 16.2 Hz), 2.53-2.40 (2 H, m), 2.17 (3 H, s), 1.97-1.74 (2 H, m), 1.68 (1 H, brs, D_2O exchangeable); FABMS *m/z* 152 (M^+).

5-Benzyloxy-1-methyl-4,5,6,7-tetrahydroisobenzofuran 22 In a similar manner to the synthesis of **11**, **22** (137 mg, quant.) was obtained as a colorless oil from **21** (86.2 mg, 0.57 mmol). IR ν_{max} (neat) cm^{-1} 2930, 2860; ^{1}H-NMR ($CDCl_3$) δ 7.37-7.27 (5 H, m), 7.04 (1 H, s), 4.61 (2 H, s), 3.81-3.72 (1 H, m), 2.87 (1 H, dd, J = 4.8, 15.5 Hz), 2.69-2.53 (2 H, m), 2.46-2.35 (1 H, m), 2.16 (3 H, s), 2.04-1.77 (2 H, m); FABMS *m/z* 243 ($M+H^+$); HR FABMS calcd for $C_{16}H_{19}O_2$ ($M+H^+$) 243.1385, found 243.1382.

1-(6-Benzyloxy-3-methyl-4,5,6,7-tetrahydro)isobenzofuraldehyde 23 In a similar manner to the synthesis of **12**, **23** (64.8 mg, 85%) was obtained as a yellow oil from **22** (68.6 mg, 0.28 mmol). IR ν_{max} (neat) cm^{-1} 2930, 2850, 1660; ^{1}H-NMR ($CDCl_3$) δ 9.56 (1 H, s), 7.35-7.27 (5 H, m), 4.61 (2 H, s), 3.94-3.86 (1 H, m), 3.10 (1 H, dd, J = 4.8, 17.8 Hz), 3.00 (1 H, dd, J = 4.8, 17.8 Hz), 2.71-2.60 (1 H, m), 2.49-2.39 (1 H, m), 2.28 (3 H, s), 2.04-1.87 (4 H, m); FABMS *m/z* 271 ($M+H^+$); HR FABMS calcd for $C_{17}H_{19}O_3$ ($M+H^+$) 271.1334, found 271.1332.

***N*-propargyl-1-(6-benzyloxy-3-methyl-4,5,6,7-tetrahydro)isobenzofurfurylamine 24** In a similar manner to the synthesis of **13**, **24** (42.0 mg, 59%) was obtained as a yellow oil from **23** (62.3 mg, 0.23 mmol). IR ν_{max} (neat) cm^{-1} 3290, 2940, 2850; ^{1}H-NMR ($CDCl_3$) δ 7.38-7.26 (5 H, m), 4.61 (2 H, d, J = 1.3 Hz), 3.81-3.73 (1 H, m), 3.75 (2 H, s), 3.40 (2 H, d, J = 2.3 Hz), 2.84 (2 H, dd, J = 4.6, 15.5 Hz), 2.66-2.51 (2 H, m), 2.43-2.32 (1 H, m), 2.23 (1 H, t, J = 2.3 Hz), 2.15 (3 H, s), 1.99-1.91 (1 H, m), 1.89-1.78 (1 H, m), 1.56 (1 H, brs); FABMS *m/z* 332 ($M+Na^+$); HR FABMS calcd for $C_{20}H_{22}O_2N$ ($M-H^+$) 308.1650, found 308.1663.

***N*-*t*-Butoxycarbonyl-*N*-propargyl-1-(6-benzyloxy-3-methyl-4,5,6,7-tetrahydro)isobenzofurfurylamine 25** In a similar manner to the synthesis of **14**, **25** (52.2 mg, quant.)was obtained as a colorless

oil from **24** (42.0 mg, 0.14 mmol). IR ν max (neat) cm^{-1} 3300, 2990, 2940, 2120, 1700; ^{1}H-NMR ($CDCl_3$) δ 7.37-7.26 (5 H, m), 4.60 (2 H, s), 3.98 (2 H, brs), 3.79-3.74 (1 H, m), 2.84 (1 H, dd, *J* = 4.6, 15.8 Hz), 2.63-2.54 (2 H, m), 2.42-2.34 (1 H, m), 2.18 (1 H, t, *J* = 2.3 Hz), 2.13 (3 H, s), 1.90-1.82 (2 H, m), 1.49 (9 H, s); FABMS *m/z* 409 (M^+); HR FABMS calcd for $C_{25}H_{31}O_4N$ (M^+) 409.2253, found 409.2252.

***N*-*t*-Butoxycarbonyl-8-benzyloxy-5-hydroxy-5-methyl-4,5,6,7,8,9-hexahydrobenzo[*e*]isoindole 27** A solution of potassium *t*-butoxide (65.3 mg, 0.58 mmol) in *t*-butanol (2 mL) was refluxed for 30 min under argon. The resulting solution was cooled to 40 °C and a solution of **25** (47.6 mg, 0.121 mmol) in *t*-butanol (2 mL) was added dropwise. The reaction mixture was refluxed for 30 min under argon. Saturated ammonium chloride solution was added to the resulting mixture and the mixture was extracted with ether. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography [hexane-ethyl acetate (4:1)] afforded crude **27** (23.7 mg, 50%) as a pale yellow oil.

***N*-*t*-Butoxycarbonyl-9-benzyloxy-6-methyl-2,3-dimethoxycarbonyl-1,4,7,8,9,10-hexahydro-1,4-iminophenanthrene 29** A solution of **27** (23.7 mg, 0.058 mmol) in dry methylene chloride (2 mL) was treated with dimethyl acetylenedicarboxylate (0.014 mL, 0.12 mmol) and methyl orthoformate (0.013 mL, 0.12 mmol) in the presence of a catalytic amount of pyridinium *p*-toluenesulfonic acid under argon. The resulting mixture was refluxed for 1.5 hr. Saturated sodium bicarbonate solution was added to the residue and the mixture was extracted with methylene chloride. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography [hexane-ethyl acetate (4:1)] afforded **29** (22.3 mg, 72%) as a yellow solid. mp 45 °C; IR ν max (KBr) cm^{-1} 2930, 1710; ^{1}H-NMR ($CDCl_3$) δ 7.40-7.27 (7 H, m), 7.09 (1 H, s), 5.81 (1 H, brs), 5.71 (1 H, s), 4.66 (2 H, s), 3.88-3.80 (1 H, m), 3.78 (6 H, s), 3.23 (1 H, dd, *J* = 4.1, 16.3 Hz), 3.01-2.91 (1 H, m), 2.88-2.76 (1 H, m), 2.59-2.52 (1 H, m), 2.15 (3 H, s), 2.14-2.05 (1 H, m), 1.98-1.82 (1 H, m), 1.39 (9 H, s); FABMS *m/z* 534 ($M+H^+$); HR FABMS calcd for $C_{31}H_{36}O_7N$ ($M+H^+$) 534.2491, found 534.2522.

4,5,6,7-Tetrahydrobenzofuran-7-one 31 A solution of 1,2-cyclohexanedione **30** (2.14 g, 19.1 mmol) in water (18 mL) was treated with 40% chloroacetaldehyde solution (4.00 mL, 20.4 mmol). The reaction mixture was stirred at r.t. for 28 h. Ethyl acetate (20 mL) was added and the resulting mixture was acidified to pH 1 with sulfuric acid. The reaction mixture was stirred at r.t. for 1 h. Saturated sodium bicarbonate solution was added and the mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography [hexane-ethyl acetate (2:1)] afforded **31** (1.69 g, 65%) as colorless needles. mp 49 °C; IR ν max (KBr) cm^{-1} 2950, 16600; ^{1}H-NMR ($CDCl_3$) δ 7.54 (1 H, d, *J* = 1.7 Hz), 6.40 (1 H, d, *J* = 1.7 Hz), 2.76 (2 H, d, *J* = 6.0 Hz), 2.57-2.52 (2 H, m), 2.18-2.09 (2 H, m); FABMS *m/z* 136 (M^+).

4,5,6,7-Tetrahydrobenzofuran-7-one oxime 32 A solution of **31** (902 mg, 6.63 mmol) in ethanol (20 mL) was treated with hydroxylamine hydrochloride (1.84 g, 26.5 mmol) and sodium bicarbonate (2.23 g, 26.5 mmol). The resulting mixture was refluxed for 3 hr. The solvent was removed in vacuo. Saturated sodium

bicarbonate solution was added to the residue and the mixture was extracted with ether. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography [hexane-ethyl acetate (2:1)] afforded **32** (656 mg, 66%) as colorless needles. mp 165 °C; IR ν_{max} (KBr) cm^{-1} 3250, 2930, 2850, 1640; ^{1}H-NMR ($CDCl_3$) δ 8.35-7.70 (1 H, brs), 7.37 (1 H, d, J = 2.0 Hz), 6.31 (1 H, d, J = 2.0 Hz), 2.77 (2 H, t, J = 6.6 Hz), 2.59 (2 H, t, J = 6.1 Hz), 1.97-1.88 (2 H, m); FABMS *m/z* 151 (M^+).

7-Amino-4,5,6,7-tetrahydrobenzofuran 33 A solution of **32** (230 mg, 1.52 mmol) in dry tetrahydrofuran (4 mL) was treated with lithium aluminiumhydride (173 mg, 4.57 mmol) at 0 °C. The resulting mixture was stirred at 40 °C for 3 hr under argon. The reaction mixture was quenched with a few drops of water and ether was added. The combined organic layer was filtered and the solvent was removed in vacuo to give crude **33**.

***N*-*t*-Butoxycarbonyl-7-amino-4,5,6,7-tetrahydrobenzofuran 34** A solution of crude **33** in dry methylene chloride (4 mL) was treated with triethylamine (1.06 mL, 7.62 mmol). Di-*t*-butyl dicarbonate (0.70 mL, 3.05 mmol) was added dropwise to the reaction mixture and the resulting mixture was stirred at r.t. for 3 h under argon. Water was added to the resulting mixture and the mixture was extracted with methylene chloride. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography [hexane-ethyl acetate (8:1)] afforded **34** (356 mg, 98%) as a colorless solid. IR ν_{max} (KBr) cm^{-1} 3370, 3300, 2880, 1680; ^{1}H-NMR ($CDCl_3$) δ 7.29 (1 H, d, J = 2.0 Hz), 6.18 (1 H, d, J = 2.0 Hz), 4.77 (1 H, brs), 2.50-2.34 (2 H, m), 2.05-1.97 (1 H, m), 1.89-1.85 (1 H, m), 1.84-1.70 (2 H, m), 1.63 (1 H, brs, D_2O exchangeable), 1.47 (9 H, s); FABMS *m/z* 238 ($M+H^+$), 260 ($M+Na^+$).

***N*-*t*-Butoxycarbonyl-*N*-propargyl-7-amino-4,5,6,7-tetrahydrobenzofuran 35** A solution of **34** (158 mg, 0.67 mmol) in dry dimethylformamide (3 mL) was treated with sodium hydride (60%, 53.4 mg, 1.33 mmol) under argon. The resulting mixture was stirred at 0 °C for 1 h. Propargyl bromide (0.10 mL, 1.33 mmol) was added dropwise to the reaction mixture and the resulting mixture was stirred at r.t. for 3 h under argon. Saturated ammonium chloride solution was added and the mixture was extracted with methylene chloride. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography [hexane-ethyl acetate (12:1)] afforded **35** (145 mg, 79%) as a colorless oil. IR ν_{max} (neat) cm^{-1} 3290, 2920, 2840, 2110, 1680; ^{1}H-NMR ($CDCl_3$) δ 7.29 (1 H, dd, J = 0.7, 2.0 Hz), 6.21 (1 H, d, J = 2.0 Hz), 5.18 (1 H, brd), 4.00 (1 H, brs), 3.49 (1 H, brd), 2.57-2.36 (2 H, m), 2.19 (1 H, t, J = 2.6 Hz), 2.15-1.94 (3 H, m), 1.79-1.65 (1 H, m), 1.49 (9 H, s); FABMS *m/z* 276 ($M+H^+$); HR FABMS calcd for $C_{16}H_{22}O_3N$ 276.1600, found 276.1598.

***N*-*t*-Butoxycarbonyl-4-hydroxy-3,4,6,7,8-pentahydrobenzo[*cd*]isoindole 37** In a similar manner to the synthesis of **27**, **37** (35.8 mg, 66%) was obtained as a colorless oil from **35** (53.9 mg, 0.20 mmol). IR ν_{max} (neat) cm^{-1} 3440, 3000, 2950, 1740; ^{1}H-NMR ($CDCl_3$) δ 6.94 (1 H, s), 5.52 (1 H, d, J = 4.6 Hz), 4.50 (1 H, brs), 2.91 (2 H, dd, J = 5.7, 11.6 Hz), 2.82 (2 H, dd, J = 1.3, 4.9 Hz), 2.37 (2 H, t, J = 6.1 Hz), 2.05-1.81 (2 H, m), 1.58 (10 H, s); FABMS *m/z* 276 ($M+H^+$); HR FABMS calcd for $C_{16}H_{22}O_3N$

276.1600, found 276.1603.

***N*-*t*-Butoxycarbonyl-9-benzyloxy-6-methyl-2,3-dimethoxycarbonyl-1,4,7,8,9,10-hexahydro-1,4-iminophenanthrene 39** In a similar manner to the synthesis of **29**, **39** (33.8 mg, 86%) was obtained as a colorless oil from **27** (27.3 mg, 0.10 mmol). ^{1}H-NMR ($CDCl_3$) δ 7.24 (1 H, d, J = 6.9 Hz), 7.02-6.97 (1 H, m), 6.86 (1 H, dd, J = 0.7, 7.9 Hz), 5.76 (1 H, s), 3.82 (3 H, s), 3.76 (3 H, s), 2.95 (1 H, dt, J = 3.3, 14.2 Hz), 2.73 (1 H, ddd, J = 2.3, 5.6, 16.8 Hz), 2.61 (1 H, ddd, J = 5.0, 11.4, 16.8 Hz), 2.33 (1 H, dt, J = 3.3, 14.2 Hz), 2.16-2.08 (1 H, m), 1.79-1.67 (1 H, m), 1.45 (9 H, s); FABMS *m/z* 400 ($M+H^+$); HR FABMS calcd for $C_{22}H_{26}O_6N$ 400.1760, found 400.1758.

REFERENCES

1 (a) Bonnett, R.; Brown, R. F. C. *J. Chem. Soc., Chem. Commun.*, **1972**, 393. (b) Bonnett, R.; Brown, R. F. C.; Smith, R. G. *J. Chem. Soc., Perkin Trans I*, **1973**, 1432. (c) Bornstein, J.; Remy, D. E.; Shields, J. E. *J. Chem. Soc., Chem. Commun.*, **1973**, 1149. (d) Priestley, G. M.; Warrener, R. N. *Tetrahedron Lett.*, **1972**, *13*, 4295.

2 (a) Beeley, L. J.; Berge, J. M.; Chapman, H.; Hieble, P.; Kelly, J.; Naselsky, D. P.; Rockell, C. M.;Young, P. W. *Bioorg. Med. Chem.*, **1995**, *3*, 1693. (b) Schubert-Zsilavecz, M.; Schramm, H. W. *Liebigs Ann. Chem.*, **1991**, 973.

3 Lee, M.; Moritomo, H.; Kanematsu, K. *J. Chem. Soc., Chem.Commun.*, **1994**, 1535.

4 (a) Hayakawa, K.; Yamaguchi, Y.; Kanematsu K. *Tetrahedron Lett.*, **1985**, *26*, 2689. (b) Yamaguchi, Y.; Yamada, H.; Hayakawa, K.; Kanematsu, K. *J. Org. Chem.*, **1987**, *52*, 2040. (c) Yamaguchi, Y.; Hayakawa, K.; Kanematsu, K. *J. Chem. Soc., Chem. Commun.*, **1987**, 515. (d) Yamaguchi, Y.; Tatsuta, N.; Hayakawa, K.; Kanematsu, K. *ibid.*, **1989** 470. (e) Yamaguchi, Y.; Tatsuta, N.; Soejima, S.; Hayakawa, K.; Kanematsu, K. *Heterocycles*, **1990**, *30*, 223.

5 Remy, D. E.; Bissett, F. H.; Bornstein, J. *J. Org. Chem.*, **1978**, *43*, 4469.

6 Matsumoto, M.; Watanabe, N. *Heterocycles*, **1984**, *22*, 2313.

7 Jutz, C. *Adv. Org. Chem.*, **1976**, *9*, pt. 1, 225-342.

8 Harris, R. B.; Wilson, I. B. *Tetrahedron Lett.*, **1983**, *24*, 231.

(*Received in Japan* 7 *March* 1996; *accepted* 15 *April* 1996)