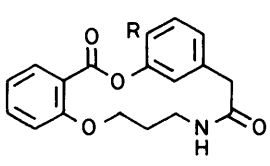
Synthesis of Novel Macrocyclic Lactones with Potential Pharmacological Activity

Keith Smith, Ian K. Morris,* and (in part) Philip G. Owen
Department of Chemistry, University College of Swansea, Singleton Park, Swansea SA2 8PP
Robert J. Bass
Pfizer Central Research, Sandwich, Kent, CT13 9NJ

The total syntheses of four 14-membered ring lactones, (**1a**), (**2a**), (**22**), and (**23**), are described. The starting materials are the appropriate 2-hydroxybenzoic or (2-hydroxyphenyl)acetic acids and the final step in each case involves lactonization using a modification of the Corey pyridinethiol ester procedure.

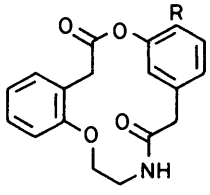
Since the 1950s many macrocyclic lactones have been isolated from natural sources[1] and these macrolides exhibit an extraordinarily diverse range of biological activities. Some have proved to be of considerable medicinal importance, for example antibiotics such as erythromycins A and B, and zearalenone, which has pronounced anabolic and uterotrophic activity.

In an effort to obtain novel macrocyclic lactones with potentially useful pharmacological properties the 14-membered types (**1**) and (**2**) were selected for synthesis. Selective reduction of the lactam group in (**1**) and (**2**) would give macrolides incorporating a phenylethylamine or hydroxyphenylethylamine unit which would be expected to have interesting properties.



(**1**)

a; R = H
b; R = OH

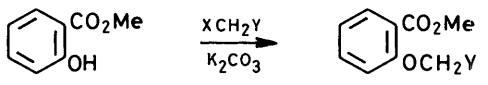


(**2**)

Additionally, the conformational possibilities arising from the inevitable *cisoid* arrangement of the Ar–C–C–N unit of (**1**) compared to the alternative *cisoid* or *transoid* arrangement of (**2**) would provide some additional insight into the importance of stereochemistry on the activity of the corresponding amines.

Previous studies have shown that it is possible to develop useful drugs from natural catecholamine neurotransmitters by appropriate synthetic modification.[2,3] Whereas natural catecholamines are relatively non-selective in receptor interactions, and are also metabolised and inactivated leading to erratic oral absorptions, modification of the catechol function and variation of the amine substituent can improve receptor selectivity and metabolic stability. Such modifications may also increase the ease of transport across various physiological barriers, the active catechol being released subsequently by enzymic cleavage of the protecting group(s).

Synthetic Approach to the Target Lactone (**1a**).—Our approach to the synthesis of the target lactone (**1a**), the simplest macrocylic lactone possessing all the main structural features for our target macrolides, consisted of four major steps; (*a*) addition of a three-carbon unit with an appropriate terminal functionality to the phenolic oxygen of methyl salicylate; (*b*) conversion of the terminal functionality into an amino group; (*c*) reaction of the amino group with an appropriately substituted phenylacetic acid; and (*d*) removal of the protecting groups and subsequent cyclisation to the target lactone.



(**3**)

a; X = Cl, Y = CH_2CN	0%
b; X = Br, Y = CH_2CH_2OH	70%[4]
c; X = Br, Y = CH_2CH_2Br	50%
d; X = Br, Y = phthalimido CH_2CH_2	95%
e; X = Br, Y = $CH{=}CH_2$	95%
f; X = Cl, Y = $CH_2CH(OEt)_2$	59%

Scheme 1.

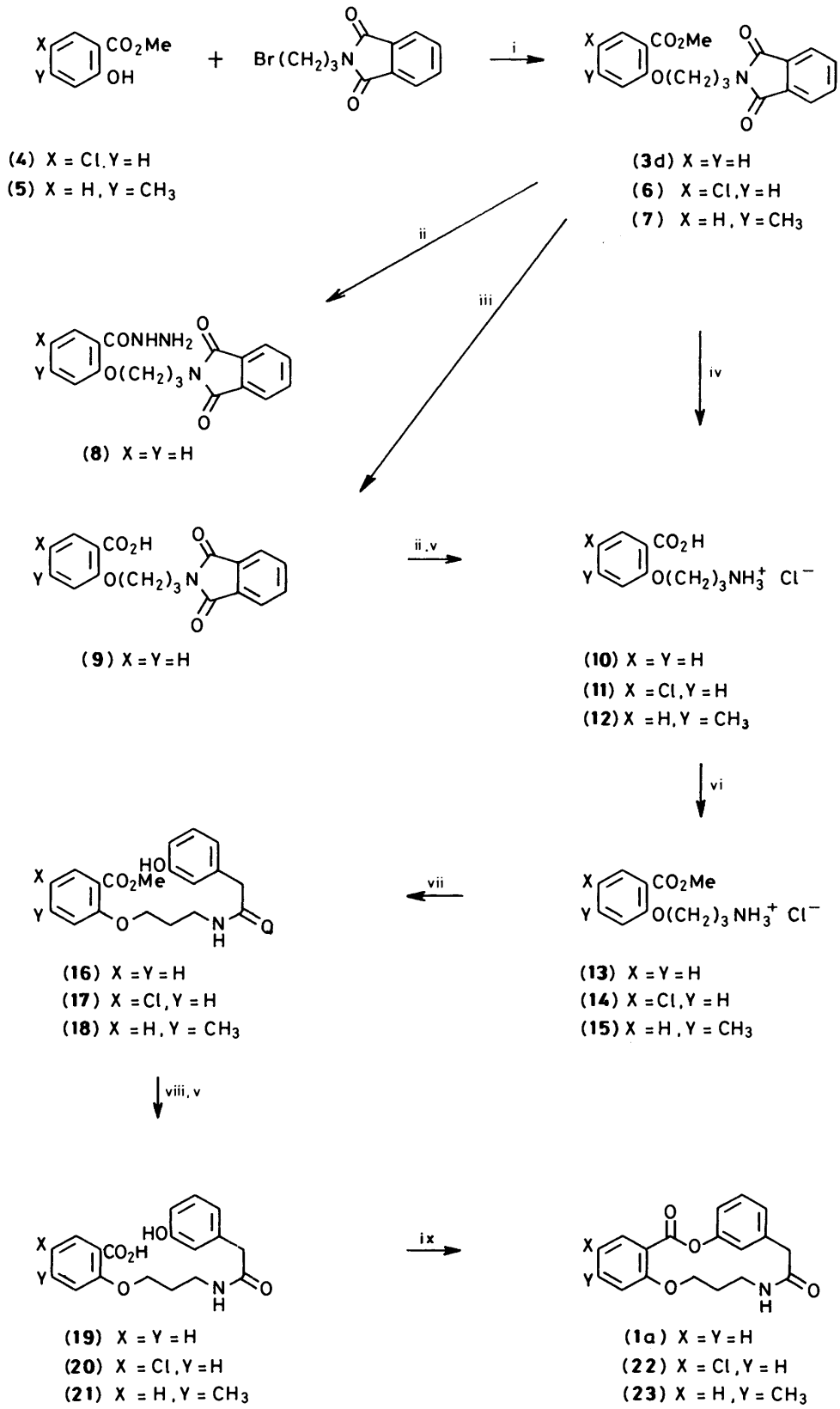
Surprisingly, few 3-substituted propyl ethers of methyl salicylate have appeared in the chemical literature. Thus, several novel compounds of this type were prepared in moderate to good yields [Scheme 1; compounds (**3b**), (**3c**), (**3d**), and (**3f**)]. All of these compounds were prepared by a Williamson ether synthesis, the reactants being refluxed with dry K_2CO_3 in acetone or DMF until the reaction was shown to be complete by t.l.c. The allyl ether (**3e**) was similarly prepared but attempts to produce a 2-cyanoethyl ether (**3a**) in a similar way, and all attempts at Michael-type reactions, for example between acrylonitrile or propenal and methyl salicylate, were unsuccessful.

The high yield found for the synthesis of 2-[3-(*N*-phthalimido)propoxy]benzoic acid methyl ester (**3d**) appeared promising for the preparation of (**1a**). This approach was therefore adopted, and the complete route is shown in Scheme 2 (X = Y = H).

Hydrazinolysis[5] of (**3d**) proved to be ineffective due to extensive nucleophilic attack at the methyl ester function to give the corresponding hydrazide (**8**). However, simple hydrolysis of (**3d**) with hydrochloric acid under reflux for 48 h provided the amino acid (**10**) in 70% yield. A shorter (*ca.* 1 h) acid hydrolysis resulted in selective cleavage of the ester group to give the acid (**9**). Hydrazinolysis of (**9**) provided an alternative route to (**10**). Treatment of (**10**) with thionyl chloride in methanol resulted in quantitative conversion into the ester (**13**).

3-Hydroxyphenylacetic acid was coupled with (**13**) with the aid of the water-soluble 1-(3-dimethylaminopropyl)-3-ethylcarbodi-imide,[6] producing (**16**) in 65% yield. Hydroxy protection of the *m*-hydroxyphenylacetic acid was not found to be necessary. Subsequent hydrolysis of the methyl ester function in (**16**) provided the hydroxy acid (**19**) in good yield.

There is a vast array of methods in the literature for the cyclization of hydroxy acids.[1] Preliminary comparative trials with a model system, (the 9-hydroxynonyl ether of salicylic acid) suggested that the optimum lactonization technique for these



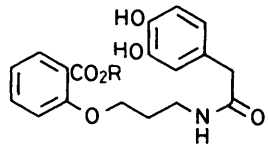
Scheme 2. *Reagents:* i, K_2CO_3, heat; ii, H_2NNH_2; iii, HCl, heat, 1 h; iv, HCl, heat, 48 h; v, dilute HCl; vi, MeOH, $SOCl_2$; vii, *m*-hydroxyphenylacetic acid, $CH_3CH_2N{=}C{=}NCH_2CH_2CH_2NMe_2{\cdot}HCl$; viii, aq. OH^-; ix, di-2-pyridyl disulphide + Ph_3P

systems would be the method of Corey *et al.*, involving double activation of the seco acid through a pyridinethiol ester intermediate prior to cyclization.[7] This extremely mild lactonization technique is well documented and has previously been used in the synthesis of many complex polyfunctional lactones.[1] However, we know of no previous examples in which the nucleophilic entity is a phenol.

Initial attempts to cyclize the hydroxy acid (**19**) by this thiol ester activation method encountered problems due to the insolubility of the hydroxy acid in aprotic nonpolar solvents. This problem was overcome by initially forming the intermediate pyridine-2-thiol ester in 1,4-dioxane; unlike the starting material, this was soluble in xylene. Slow injection of a xylene solution into an excess of refluxing xylene under high dilution conditions successfully completed the cyclization, giving the target macrocyclic lactone (**1a**) in 53% yield.

Synthesis of Substituted Analogues of the Macrocyclic Lactone (**1a**).—To provide further examples of this novel system, lactones (**22**) and (**23**) were synthesized analogously from 5-chloro-2-hydroxybenzoic acid (**4**) and 2-hydroxy-4-methylbenzoic acid (**5**) respectively in comparable yields (see Scheme 2).

However, our attempted synthesis of a catechol derivative of the initial target lactone [*i.e.* (**1b**)] was unsuccessful. We hoped that the final cyclization could be achieved without need for protection of one of the phenolic hydroxy groups of (**24b**), because of conformational preference for attachment *via* the *meta*-hydroxy rather than the *para*. Synthesis of the ester (**24a**) was achieved uneventfully. However, the free acid (**24b**) proved to be extremely unstable, quickly decomposing after isolation.



(**24**)

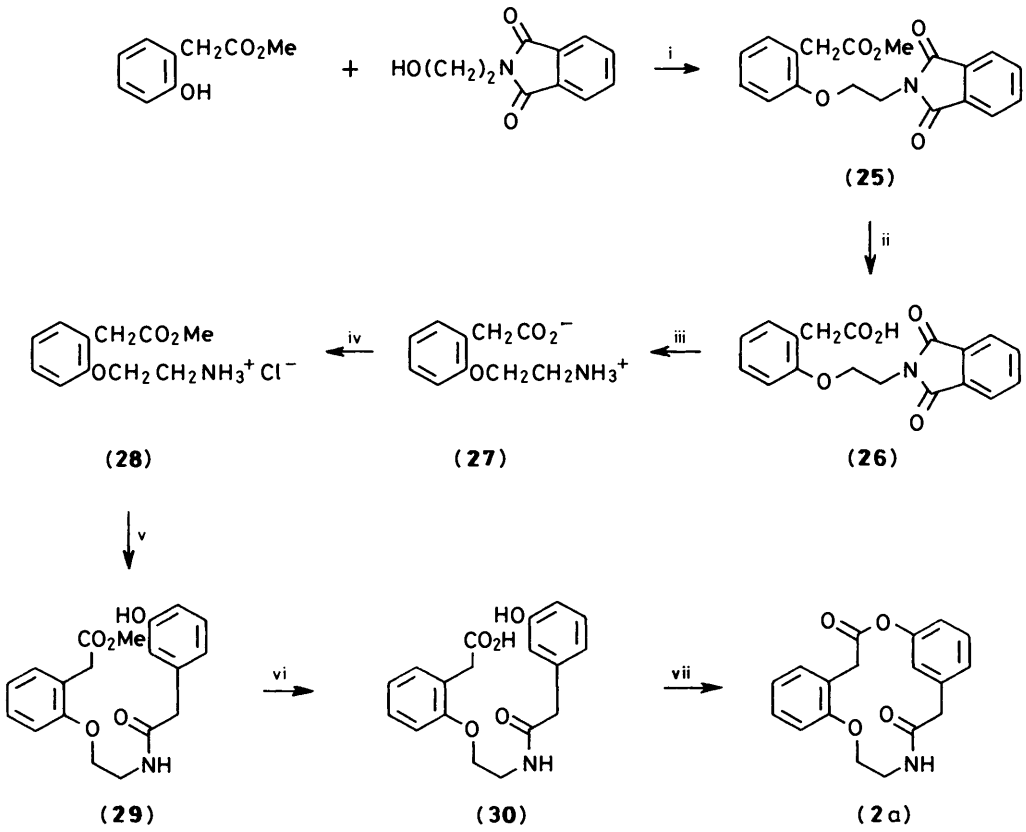
a; R = Me

b; R = H

Synthetic Approaches to the Target Lactone (**2a**).—A synthetic route (Scheme 3) to the lactone (**2a**) was conveniently adapted from the knowledge gained in the synthesis of lactones of type (**1**). The first step required formation of the alkyl aryl ether (**25**). However, the reaction between methyl (2-hydroxyphenyl)acetate and *N*-(2-bromoethyl)phthalimide failed to produce (**25**).

This problem was overcome by using *N*-(2-hydroxyethyl)-phthalimide and diethyl azodicarboxylate (DEAD), a reagent capable of coupling phenols and alcohols to give alkyl aryl ethers.[8] The resulting reaction between *N*-(2-hydroxyethyl)-phthalimide[9] and methyl *m*-hydroxyphenylacetate using DEAD as the coupling agent produced (**25**) in an optimal yield of 50%.

Both acid and base hydrolyses of the phthalimide function in (**25**) failed. Thus, the methyl ester group in (**25**) was first hydrolysed using mild acid conditions, and the resulting carboxylic acid (**26**) was then treated with hydrazine hydrate[4] to give the required amino acid (**27**) in good yield. Treatment of (**27**) with thionyl chloride and methanol gave the methyl ester (**28**), thus providing the carboxylate protection needed prior to the coupling of (**28**) with *m*-hydroxyphenylacetic acid. Coupling



Scheme 3. *Reagents:* i, DEAD, Ph_3P; ii, HCl, heat, 1 h; iii, H_2NNH_2, AcOH; iv, MeOH, $SOCl_2$; v, *m*-hydroxyphenylacetic acid + $CH_3CH_2N{=}C{=}NCH_2CH_2CH_2NMe_2{\cdot}HCl$; vi, aq. NaOH; vii, di-2-pyridyl disulphide + Ph_3P

with 1-(3-dimethylaminopropyl)-3-ethylcarbodi-imide gave the protected seco acid (**29**), which on treatment with mild base gave the hydroxy acid (**30**).

The adaptation of the Corey lactonization technique[7] used for the synthesis of the lactone (**8**) was used again for the cyclization of (**30**). This gave the target lactone (**2a**) in an isolated yield of 20% (not increased by variation of reaction conditions). Nevertheless, the reaction has given access to this novel lactone type.

Conclusion.—A number of macrocyclic lactones also possessing a lactam group have been synthesized. The syntheses of other related systems are under investigation and will be reported separately.

Experimental

Melting points were measured on a hot-stage apparatus and are uncorrected. Kieselgel 60 (230—400 mesh) silica gel (Merck) was used for column chromatography and analytical t.l.c. was performed using Merck silica gel 60 F254 pre-coated sheets (0.2 mm). ^{1}H N.m.r. spectra were mostly obtained on a Varian HA-100 MHz spectrometer. In some cases the quantity of material available necessitated the use of an XL-100 MHz FT spectrometer. ^{13}C N.m.r. spectra were invariably obtained on a Varian XL-100 MHz FT spectrometer. I.r. spectra were obtained on a Pye Unicam SP1050 spectrophotometer. Solids were run as KBr discs, liquids were run neat between NaCl plates, and thick oils and gums were run as Nujol mulls. Mass spectra were measured using a modified Kratos MS9 instrument.

Methyl 2-[3-(N-*Phthalimido*)*propoxy*]*benzoate* (**3d**).—*N*-(3-Bromopropyl)phthalimide (10 mmol, 2.68 g) and methyl salicylate (10 mmol, 1.52 g), together with a large excess of dry potassium carbonate (5 g), were refluxed in acetone (50 ml), whilst being vigorously stirred, for 24 h. Removal of the acetone under reduced pressure gave an off-white solid. Chloroform (50 ml) was added to this solid in order to dissolve the organic material, and the mixture was filtered. Removal of the chloroform from the filtrate produced a white solid which after recrystallization from acetone–ethyl acetate gave (**3d**) (3.15 g, 93% yield), m.p. 137—138 °C; $\nu_{max.}$ (KBr disc) 1 775, 1 715, and 1 605 cm^{-1}; δ_H($CDCl_3$) 2.2 (2 H, quint., *J* 6 Hz), 3.85 (3 H, s), 3.9 (2 H, t, *J* 6 Hz), 4.05 (2 H, t, *J* 6 Hz), and 6.5—7.85 (8 H, m); δ_C($CDCl_3$) 28.5, 35.4, 51.9, 66.5, 113.2, 120.4, 120.5, 123.1, 131.8, 132.2, 133.4, 133.8, 158.2, 166.9, and 168.2; *m/z* 339 (M^+, 0.6%), 188 (100), 160 (55), 30 (17), 120 (13), and 41 (23) (Found: C, 67.5; H, 5.2; N, 0.4%; M^+, 339.1107. $C_{19}H_{17}NO_5$ requires C, 67.3; H, 5.0; N, 4.1%; M^+, 339.1106). Preparations of compounds (**3a**) to (**3f**) were carried out in a similar manner.

Methyl 5-*Chloro*-2-[3-(N-*phthalimido*)*propoxy*]*benzoate* (**6**).—The synthesis of (**6**) was identical with that of (**3d**), previously described (yield 90%); m.p. 144—145 °C; $\nu_{max.}$ (KBr disc) 1 775, 1 720, and 1 600 cm^{-1}; δ_H($CDCl_3$) 2.2 (2 H, quint., *J* 6 Hz), 3.75—4.95 (5 H, m), 4.97—4.15 (2 H, t, *J* 6 Hz), 6.85 (1 H, d, *J* 8 Hz), and 7.32 (1 H, dd, *J* 1.5 and 9 Hz); δ_C($CDCl_3$) 28.5, 35.3, 52.2, 66.9, 75.9, 77.2, 78.5, 114.6, 121.6, 123.1, 125.3, 131.5, 132.1, 133.0, 133.9, 156.9, 165.5, and 168.2; *m/z* 373 ($M^{+\bullet}$, 0.9%), 188 (100), 160 (61), 154 (22), 43 (26), and 41 (22) (Found: C, 60.8; H, 4.2; N, 3.9. $C_{19}H_{16}ClNO_5$ requires C, 61.0; H, 4.3; N, 3.8%).

Methyl 4-*Methyl*-2-[3-(N-*phthalimido*)*propoxy*]*benzoate* (**7**).—The synthesis of (**7**) was identical with that of (**3d**) previously described (yield 87%); m.p. 116 °C; $\nu_{max.}$ (KBr disc) 1 775, 1 720, and 1 605 cm^{-1}; δ_H($CDCl_3$) 2.2 (2 H, quint., *J* 6 Hz), 2.35 (3 H, s), 3.8—4.2 (7 H, m), 6.6—6.7 (2 H, m), and 7.55—7.9 (5 H, m); δ_C($CDCl_3$) 21.8, 28.6, 35.5, 51.7, 66.5, 75.9, 77.1, 78.4, 114.0, 117.4, 119.4, 121.3, 123.1, 132.0, 132.2, 133.8; 144.4, 158.5, and 168.3; *m/z* 353 ($M^{+\bullet}$, 2.6%), 189 (13), 188 (100), 160 (44), 41 (13), and 28 (18) (Found: C, 68.1; H, 5.6; N, 3.8. $C_{20}H_{19}NO_5$ requires C, 68.0; H, 5.4; N, 4.0%).

2-[3-(N-*Phthalimido*)*propoxy*]*benzoic Acid* (**9**).—Compound (**3d**) (1.52 g, 4.5 mmol) was dissolved in 1,4-dioxane (25 ml) and concentrated hydrochloric acid (10 ml). The solution was heated at reflux temperature until t.l.c. (silica, MeOH) indicated complete conversion of the ester (R_F, 0.83) into the acid (R_F, 0.71). Typically the reaction period was in the region of 1 h at reflux temperature. The 1,4-dioxane and hydrochloric acid were removed under reduced pressure to leave a white solid. Recrystallization from methanol provided a white crystalline solid (**9**) (1.14 g, 78%), m.p. 160—161 °C; $\nu_{max.}$ (KBr disc) 1 700, 1 730, and 3 000 cm^{-1}; δ_H([$^2H_6$]DMSO) 2.1 (2 H, quint., *J* 6.5 Hz), 3.8 (2 H, t, *J* 6.5 Hz), 4.1 (2 H, t, *J* 6.5 Hz), 6.85—7.59 (3 H, m), and 7.65 (1 H, dd, *J* 2 and 8 Hz); *m/z* 325 (M^+, 1.8%), 188 (100), 160 (90), 130 (27), and 41 (28) (Found: C, 66.8; H, 4.7; N, 4.5. $C_{18}H_{15}NO_5$ requires C, 66.5; H, 4.6; N, 4.3%).

2-(3-*Aminopropoxy*)*benzoic Acid Hydrochloride* (**10**) *by Acid Hydrolysis.*—Compound (**3d**) (3.8 g, 11 mmol) was dissolved in 1,4-dioxane (25 ml) and concentrated hydrochloric acid (10 ml). This solution was then heated at reflux temperature for 48 h. The 1,4-dioxane and hydrochloric acid were both removed under reduced pressure to give a colourless gum. The gum was then triturated with acetone causing phthalic acid to dissolve and leaving a white precipitate which was separated. Recrystallization of this solid from acetone–methanol provided the title compound (**10**) (1.78 g, 70%), m.p. 162—163 °C; $\nu_{max.}$ (KBr disc) 3 000, 1 700, 1 600, and 1 510 cm^{-1}; δ_H([$^2H_6$]DMSO) 2.15 (2 H, quint., *J* 6 Hz), 3.1 (2 H, t, *J* 6 Hz), 4.2 (2 H, t, *J* 6 Hz), 6.9—7.65 (3 H, m), 7.75 (1 H, dd, *J* 1.5 and 7 Hz), 8.5 (3 H, br, exch.), and 11.2 (1 H, br, exch.); δ_C([$^2H_6$]DMSO) 26.1, 66.9, 113.2, 120.0, 120.5, 131.3, 133.8, 157.8, and 167.6 (Found: C, 51.8; H, 6.1; H, 6.0. $C_{10}H_{14}ClNO_3$ requires C, 51.7; H, 6.1; N, 6.0%).

2-(3-*Aminopropoxy*)-5-*chlorobenzoic Acid Hydrochloride* (**11**).—The synthesis of compound (**11**) was carried out using a procedure identical with the synthesis of (**10**) previously described (yield 68%), m.p. 193—195 °C; $\nu_{max.}$ (KBr disc) 3 050, 1 725, 1 600, 1 520, and 1 210 cm^{-1}; δ_H([$^2H_6$]DMSO) 2.0 (2 H, t), 3.0 (2 H, br), 6.8—7.8 (3 H, m), and 8.2 (3 H, br, exch.); δ_C([$^2H_6$]DMSO) 26.3, 36.7, 66.8, 115.4, 122.1, 123.9, 130.2, 132.8, 156.3, and 166.0 (Found: C, 45.0; H, 4.9; N, 5.3. $C_{10}H_{13}Cl_2NO_3$ requires C, 45.1; H, 4.9; N, 5.3%).

2-(3-*Aminopropoxy*)-4-*methylbenzoic Acid Hydrochloride* (**12**).—The synthesis of (**12**) was identical with that of compound (**10**) previously described (yield 75%); m.p. 188—190 °C; $\nu_{max.}$ (KBr disc) 3 000, 1 700, 1 620, and 1 520 cm^{-1}; δ_H([$^2H_6$]DMSO) 2.2 (2 H, quint), 2.35 (3 H, s), 3.05 (2 H, t), 4.15 (2 H, t), 6.7—7.7 (3 H, m), and 8.3 (3 H, br, exch.); δ_C([$^2H_6$]DMSO) 21.3, 26.3, 37.1, 66.6, 113.8, 116.9, 121.0, 131.4, 144.4, 158.0, and 167.2 (Found: C, 53.6; H, 6.2; N, 5.5. $C_{11}H_{16}ClNO_3$ requires C, 53.5; H, 6.5; N, 5.7%).

Methyl 2-(3-*Aminopropoxy*)*benzoate Hydrochloride* (**13**).—To a stirred solution of (**10**) (1.16 g, 5.0 mmol) in methanol (15 ml) at 0 °C was slowly added, dropwise, a 3 molar excess of thionyl chloride. The solution was then warmed to 60 °C and stirred for a further 10 h. The methanol and excess thionyl chloride were removed under reduced pressure to give an off white solid. Recrystallisation from chloroform–acetone[10] produced (**13**) (0.93 g, 76%); m.p. 132—133 °C; $\nu_{max.}$ (KBr disc) 3 150, 1 705, 1 620, and 1 505 cm^{-1}; δ_H($CDCl_3$) 2.15 (2 H, quint, *J* 6 Hz), 3.1 (2

H, t, *J* 6 Hz), 3.8 (3 H, s), 4.2 (2 H, t, *J* 6 Hz), 6.9—7.5 (3 H, m), 6.67 (1 H, dd, *J* 2 and 8 Hz), 8.4 (3 H, br, exch.); $\delta_C(CDCl_3)$ 26.5, 36.4, 51.9, 65.9, 113.6, 119.6, 120.3, 130.9, 133.7, 157.5, and 166.1 (Found: C, 53.4; H, 7.0; N, 5.3. $C_{11}H_{16}ClNO_3$ requires C, 53.8; H, 6.6; N, 5.7%).

Methyl 2-(3-*Aminopropoxy*)-5-*chlorobenzoate Hydrochloride* (**14**).—The synthesis of compound (**14**) was carried out using a procedure identical with that of compound (**13**) previously described (yield 74%), m.p. 180—182 °C; $\nu_{max.}$ (KBr disc) 3 205, 1 750, 1 640, 1 600, and 1 540 cm^{-1}; $\delta_H(CDCl_3)$ 2.4 (2 H, quint. *J* 5 Hz), 3.42 (2 H, t, *J* 5 Hz), 3.95 (3 H, s), 4.25 (2 H, t, *J* 5 Hz), 6.95 (1 H, d, *J* 9 Hz), 7.32 (3 H, s), 7.52 (1 H, dd, *J* 2 and 9 Hz), and 7.97 (1 H, d, *J* 3 Hz) (Found: C, 46.9; H, 5.5; N, 4.8. $C_{11}H_{15}Cl_2NO_3$ requires C, 47.1; H, 5.4; N, 5.0%).

Methyl 2-(3-*Aminopropoxy*)-4-*methylbenzoate Hydrochloride* (**15**).—The synthesis of compound (**15**) was carried out by a procedure identical with that of compound (**13**) (81% yield), m.p. 128—130 °C; $\nu_{max.}$ (KBr disc) 3 020, 1 720, 1 620, and 1 515 cm^{-1}; $\delta_H([^2H_6]DMSO)$ 2.15 (2 H, quint., *J* 6 Hz), 2.32 (3 H, s), 3.1 (2 H, t, *J* 6 Hz), 3.8 (3 H, s), 4.2 (2 H, t, *J* 6 Hz), 6.85 (1 H, d, *J* 8 Hz), 6.97 (1 H, s), 7.65 (1 H, d, *J* 8 Hz), and 8.5 (3 H, br, exch.); $\delta_C([^2H_6]DMSO)$ 21.4, 26.6, 36.8, 51.8, 66.2, 114.2, 116.4, 121.1, 131.2, 144.7, 158.0, and 166.0 (Found: C, 55.3; H, 7.15; N, 5.1. $C_{12}H_{18}ClNO_3$ requires C, 55.5; H, 6.9; N, 5.4%).

N-[3-(2-*Methoxycarbonylphenoxy*)*propyl*]-m-*hydroxyphenylacetamide* (**16**).—Methyl 2-(3-aminopropoxy)benzoate hydrochloride (**13**) (5.0 g, 20.0 mmol), *m*-hydroxyphenylacetic acid (3.09 g, 20.0 mmol), a small excess of 1-(3-dimethylaminopropyl)-3-ethylcarbodi-imide hydrochloride (4.8 g, 25 mmol), and triethylamine (2.5 g, 25 mmol) were added to a mixture of acetonitrile and tetrahydrofuran (1:1; 100 ml). The resulting solution was stirred under nitrogen at ambient temperature for 24 h. The precipitated triethylammonium hydrochloride salt was removed and the filtrate was evaporated under reduced pressure. The resulting oil was dissolved in chloroform (75 ml). This chloroform solution was then washed successively with 3M hydrochloric acid (50 ml), 10% aqueous sodium hydrogen carbonate (50 ml), and water (50 ml) and then dried ($MgSO_4$). Removal of the chloroform left a light brown solid which was chromatographed using Kieselgel 60 silica gel and eluted with 10% propan-2-ol–chloroform. The product was recovered from the column as a white crystalline solid (4.46 g, 65% yield), m.p. 111—112 °C; $\nu_{max.}$ (KBr disc) 3 380, 1 720, 1 660, 1 600, and 1 560 cm^{-1}; $\delta_H(CDCl_3)$ 1.9 (2 H, quint., *J* 6 Hz), 3.25—3.65 (4 H, m), 3.75 (3 H, s), 3.95 (2 H, t, *J* 6 Hz), 6.55—7.5 (7 H, m), 7.85 (1 H, dd, *J* 2 and 7 Hz), and 8.6 (1 H, s, exch.); $\delta_C(CDCl_3)$ 28.4, 38.6, 42.9, 52.0, 68.4, 112.6, 114.2, 116.5, 118.5, 120.3, 129.4, 132.0, 134.3, 137.1, 157.2, 158.9, 166.3, and 172.6; *m/z* 343 (M^+, 12.6%), 204 (43), 192 (100), 121 (20), and 107 (46) (Found: C, 66.4; H, 6.5; N, 3.9. $C_{19}H_{21}NO_5$ requires C, 66.5; H, 6.2; N, 4.1%).

N-[3-(4-*Chloro*-2-*methoxycarbonylphenoxy*)*propyl*]-m-*hydroxyphenylacetamide* (**17**).—The synthesis of compound (**17**) was carried out using a procedure identical with that of (**16**) previously described (yield 68%), m.p. 129—130 °C; $\nu_{max.}$ (KBr disc) 3 350, 1 720, 1 660, and 1 560 cm^{-1}; $\delta_H([^2H_6]DMSO)$ 1.9 (2 H, quint., *J* 6 Hz), 3.1—3.45 (4 H, m), 3.8 (3 H, s), 4.0 (2 H, t, *J* 6 Hz), 6.4—7.7 (7 H, m), 8.0 (1 H, t, *J* 6 Hz, exch.), and 9.25 (1 H, s, exch.); $\delta_C(CDCl_3)$ 28.3, 38.5, 42.9, 52.3, 68.9, 114.1, 114.3, 116.4, 119.7, 120.3, 125.4, 129.5, 131.7, 133.9, 137.0, 157.2, 157.5, 165.1, and 172.6; *m/z* 377 (M^+, 2.5%), 192 (100), 108 (11.5), 107 (38), 58 (12), and 30 (23) (Found: C, 60.6; H, 5.5; N, 3.4. $C_{19}H_{20}ClNO_5$ requires C, 60.4; H, 5.4; N, 3.7%).

N-[3-(5-*Methyl*-2-*methoxycarbonylphenoxy*)*propyl*]-m-*hydroxyphenylacetamide* (**18**).—The synthesis of compound (**18**) was carried out using a procedure identical with that of compound (**16**) previously described (yield 70%), m.p. 138—139 °C; $\nu_{max.}$ (KBr disc) 3 330, 1 725, 1 650, and 1 585 cm^{-1}; $\delta_H([^2H_6]DMSO)$ 1.85 (2 H, quint., *J* 6 Hz), 2.3 (3 H, s), 3.1—3.45 (4 H, m), 3.75 (3 H, s), 4.0 (2 H, t, *J* 6 Hz), 6.5—7.15 (6 H, m), 7.6 (1 H, d, *J* 8 Hz), and 8.1 (1 H, t, *J* 6 Hz, exch.); $\delta_C([^2H_6]DMSO)$ 21.4, 28.9, 36.2, 42.5, 51.5, 66.5, 113.4, 114.0, 116.0, 119.6, 120.8, 129.0, 131.1, 137.9, 144.5, 157.3, 158.2, 166.0, and 170.2; *m/z* 357 (M^+, 2.9%), 192 (100), 135 (29), 134 (29.5), 107 (81), 77 (29.5), and 30 (32) (Found: C, 67.4; H, 6.7; N, 3.6. $C_{20}H_{23}NO_5$ requires C, 67.2; H, 6.5; N, 3.9%).

N-[3-(2-*Methoxycarbonylphenoxy*)*propyl*]3,4-*dihydroxyphenylacetamide* (**24a**).—The synthesis of compound (**24a**) was carried out in a similar manner to that of (**16**). However, owing to the susceptibility of the product to undergo slow oxidation, the reaction was carried out under nitrogen. Recrystallization of the slightly crude product obtained after column chromatography from acetone–ether provided (**24a**) (55% yield), m.p. 152—153 °C; $\nu_{max.}$ (KBr disc) 3 500, 3 330, 1 710, 1 650, and 1 555 cm^{-1}; $\delta_H([^2H_6]DMSO)$ 1.85 (2 H, quint., *J* 6 Hz), 3.1—3.4 (4 H, m), 3.8 (3 H, s), 4.0 (2 H, t, *J* 6 Hz), 6.4—7.52 (7 H, m), 7.67 (1 H, dd, *J* 1.5 and 7 Hz), 8.0 (1 H, t, exch.), and 8.6 (2 H, br, exch.); $\delta_C([^2H_6]DMSO)$ 28.8, 36.0, 41.9, 51.7, 66.4, 113.4, 115.3, 116.4, 119.7, 119.9, 120.1, 127.3, 130.8, 133.6, 143.8, 144.9, 157.8, 166.2, and 170.8; *m/z* 359 (M^+, 8.1%), 207 (100), 204 (23), 178 (29), 123 (51), and 121 (23) (Found: C, 63.8; H, 6.1; N, 3.6. $C_{19}H_{21}NO_6$ requires C, 63.5; H, 5.9; N, 4.0%).

N-[3-(2-*Carboxyphenoxy*)*propyl*]-m-*hydroxyphenylacetamide* (**19**).—To compound (**16**) (1.0 g, 2.91 mmol) was added a 3 molar excess of aqueous sodium hydroxide (366 mg in 15 ml). The compound completely dissolved after several minutes and the solution was stirred at room temperature for 5 h. Monitoring of the reaction by t.l.c. (90% CH_2Cl_2:9% propan-2-ol:1% AcOH) showed complete conversion of the ester (R_F 0.72) into the acid (R_F 0.59). The solution was then acidified with 3M HCl and the resulting precipitate extracted into chloroform. Removal of the chloroform left a white solid which after recrystallization from chloroform–acetone* produced compound (**19**) (0.79 g, 83%), m.p. 144—145 °C; $\nu_{max.}$ (KBr disc) 3 410, 3 380, 1 710, 1 620, 1 590, and 1 560 cm^{-1}; 250 MHz ^1H n.m.r., $\delta_H([^2H_6]DMSO)$ 1.9 (2 H, quint., *J* 5 Hz), 3.3 (2 H, q, *J* 5 Hz), 3.38 (2 H, s), 4.2 (2 H, t, *J* 5 Hz), 6.6—6.75 (2 H, m), 6.95—7.15 (2 H, m), 7.5 (1 H, t, *J* 8 Hz), 7.7 (1 H, dd, *J* 2 and 8 Hz), 8.15 (1 H, t, exch.), 9.2 (1 H, br, exch.), and 12.5 (1 H, br, exch); $\delta_C([^2H_6]DMSO)$ 28.7, 36.2, 42.4, 66.5, 113.3, 115.9, 119.6, 120.0, 121.1, 129.0, 130.8, 133.1, 137.8, 157.2, 157.6, 167.3 and 170.2; *m/z* 329 (M^+, 0.8%), 190 (17), 138 (48), 120 (100), 107 (29), and 92 (43) (Found: C, 65.5; H, 5.9; N, 4.3. $C_{18}H_{19}NO_5$ requires C, 65.7; H, 5.8; N, 4.3%).

N-[3-(2-*Carboxy*-4-*chlorophenoxy*)*propyl*]-m-*hydroxyphenylacetamide* (**20**).—The synthesis of compound (**20**) was carried out using a procedure identical with that previously described for compound (**19**) (yield 70%), m.p. 155—156 °C; $\nu_{max.}$ (KBr disc) 3 300, 1 720, 1 620, 1 600, 1 560, and 1 495 cm^{-1}; $\delta_H([^2H_6]DMSO)$ 1.9 (2 H, quint., *J* 6 Hz), 3.1—3.5 (4 H, m), 4.0 (2 H, t, *J* 6 Hz), 6.4—7.2 (5 H, m), 7.5 (1 H, dd, *J* 3 and 9 Hz), 7.7 (1 H, d, *J* 3 Hz), 8.1 (1 H, t, *J* 6 Hz, exch.), 9.3 (1 H, br, exch.), and 12.7 (1 H, br, exch.); $\delta_C([^2H_6]DMSO)$ 28.6, 36.1, 42.4, 67.0, 113.4, 115.2, 119.7, 122.5, 123.9, 129.1, 130.2, 132.7, 137.7, 156.5,

* *N.B.* Explosions have been reported with this mixture of solvents, so care should be exercised, although no problems were encountered here. See H. K. King, *Chem. and Ind.* (*London*), 1970, 185.

157.1, 166.1, 170.6, and 170.7; *m/z* 192 (32%), 190 (55), 156 (24), 154 (76), 107 (100), and 63 (42) (Found: C, 59.3; H, 5.1; N, 3.6. $C_{18}H_{18}ClNO_5$ requires C, 59.4; H, 4.95; H, 3.85%).

N-[3-(2-*Carboxy*-5-*methylphenoxy*)*propyl*]-m-*hydroxyphenylacetamide* (**21**).—The synthesis of compound (**21**) was carried out using a procedure identical with that previously described for compound (**19**) (yield 77%), m.p. 157—158 °C; $\nu_{max.}$ (KBr disc) 3 550, 3 320, 1 700, 1 600, and 1 245 cm^{-1}; $\delta_H([^2H_6]DMSO)$ 1.85 (2 H, quint., *J* 6 Hz), 2.3 (3 H, s), 3.1—3.5 (4 H, m), 4.0 (2 H, t, *J* 6 Hz), 6.55—7.15 (6 H, m), 7.65 (1 H, d, *J* 8 Hz), 8.1 (1 H, t, exch.), 9.4 (1 H, br, exch.), and *ca.* 12 (1 H, br, exch.); $\delta_C([^2H_6]DMSO)$ 21.3, 28.7, 36.4, 42.4, 66.7, 113.3, 113.9, 116.0, 117.7, 119.7, 120.8, 129.0, 131.1, 137.8, 144.0, 157.2, 158.0, 167.1, and 170.3; *m/z* 343 (M^+, 3.4%), 192 (82), 190 (59), 134 (100), 107 (95), and 78 (42) (Found: C, 66.7; H, 6.3; N, 4.0. $C_{19}H_{21}NO_5$ requires C, 66.5; H, 6.5; N, 4.1%).

N-[3-(2-*Carboxyphenoxy*)*propyl*]-3,4-*dihydroxyphenylacetamide* (**24b**).—The synthesis of (**24b**) was carried out in a similar manner to that of compound (**19**). However, owing to the rapid oxidation of the product when exposed to the atmosphere both the reaction and the work-up had to be carried out under a nitrogen atmosphere; $\nu_{max.}$ (KBr disc) 3 300, 1 715, and 1 605 cm^{-1} [the i.r. spectrum showed only poor resolution of bands, probably owing to the rapid oxidation of (**24b**)]; $\delta_H([^2H_6]DMSO)$ 1.85 (2 H, quint., *J* 6 Hz), 3.05—3.5 (4 H, m), 4.0 (2 H, t, *J* 6 Hz), 6.3—7.55 (6 H, m), 7.7 (1 H, dd, *J* 1.5 and 7 Hz), 8.0 (1 H, t, exch.), 9.2 (2 H, br, exch.), and *ca.* 12 (1 H, br, exch.); $\delta_C([^2H_6]DMSO)$ 28.6, 36.1, 41.8, 66.5, 113.2, 115.3, 116.3, 119.7, 120.0, 121.0, 127.3, 130.8, 133.1, 143.7, 144.8, 157.5, 167.3, and 170.9; *m/z* 345 (M^+, 1.4%), 207 (69), 138 (59), 123 (38), 120 (100), and 92 (60).

General Synthesis for the Target Macrocyclic Lactones (**1a**), (**22**), *and* (**23**).—The hydroxy acid (0.50 mmol), di-2-pyridyl disulphide [Aldrithiol-2] (0.75 mmol), and triphenylphosphine (0.75 mmol) were dissolved in 1,4-dioxane (10 ml) under nitrogen and stirred at room temperature for 5 h. The resulting yellow solution containing the pyridine-2-thiol ester was diluted with xylene (15 ml) and then slowly added from a mechanically driven syringe over 15 h to xylene (100 ml) at reflux temperature under nitrogen. Reflux was continued for an additional 15 h after complete injection of the solution. Following this reflux period the xylene and dioxane were removed under reduced pressure to give an orange gum. Trituration of this gum with ethyl acetate provided the lactone in a crude solid form which was isolated by filtration. Recrystallization of this material from THF gave the desired lactones in good yields.

Lactone (**1a**). Yield 53%, m.p. 252—254 °C; $\nu_{max.}$ (KBr disc) 3 275, 3 100, 1 750, 1 640, 1 590, and 1 230 cm^{-1}; δ_H (250 MHz; $[^2H_5]$pyridine) 2.1 (2 H, quint., *J* 5.5 Hz, $CH_2CH_2CH_2$), 3.55 (2 H, q, *J* 5.5 Hz, CH_2N), 3.65 (2 H, s, CH_2CO), 4.1 (2 H, t, *J* 5.5 Hz, OCH_2), 6.78 (1 H, d, *J* 7.5 Hz), 6.85—7.25 (5 H, m), 7.63 (1 H, dd, *J* 3 and 8 Hz), 7.91 (1 H, br s), 9.0 (1 H, vbr with fine structure, NH); *m/z* 311 (M^+, 25.5%), 204 (39), 191 (100), 134 (42), 121 (42), and 78 (49) (Found: C, 69.3; H, 5.5; N, 4.3%; M^+, 311.1157. $C_{18}H_{17}NO_4$ requires C, 69.4; H, 5.5; N, 4.5% *M*, 311.1157).

Lactone (**22**). Yield 52%, m.p. 245 °C; $\nu_{max.}$ (KBr disc) 3 280, 3 100, 1 750, 1 650, 1 590, and 1 240 cm^{-1}; $\delta_H([^2H_6]DMSO)$ 1.95 (2 H, br, quint., $CH_2CH_2CH_2$), 3.24 (2 H, br, q, CH_2N), 3.35 (2 H, s, CH_2CO), 4.0 (2 H, t, *J* 5.5 Hz, OCH_2), 6.9—7.5 (6 H, m), 7.63 (1 H, d, *J* 2.5 Hz), and 8.4 (1 H, br t, NH); *m/z* 345 (M^+, 34%), 238 (31.5), 191 (100), 155 (24), 134 (56), and 78 (56.5) (Found: C, 62.3; H, 4.6; N, 4.0. $C_{18}H_{16}ClNO_4$ requires C, 62.5; H, 4.7; N, 4.0%).

Lactone (**23**). Yield 57%, m.p. 236—238 °C; $\nu_{max.}$ (KBr disc) 3 390, 3 100, 1 745, 1 650, 1 590, 1 450, and 1 230 cm^{-1}; $\delta_H([^2H_6]DMSO)$ 1.95 (2 H, br, quint.), 2.24 (3 H, s), 3.05—3.4 (4 H, m), 3.95 (2 H, t, *J* 5.5 Hz), 6.65—7.4 (7 H, m), and 8.35 (1 H, br t, NH); *m/z* 325 (M^+, 21%), 192 (29), 191 (100), 135 (37.5), 134 (27), and 78 (34) (Found: C, 70.4: H, 6.2; N, 3.8. $C_{19}H_{19}NO_4$ requires C, 70.1; H, 5.9; N, 4.3%).

Methyl 2-[2′-(N-*Phthalimido*)*ethoxy*]*phenylacetate* (**25**).—To methyl *o*-hydroxyphenylacetate (10.00 g, 60 mmol) and *N*-(2-hydroxyethyl)phthalimide (11.46 g, 60 mmol) in THF (100 ml) was added a small excess of triphenylphosphine (18.36 g, 70 mmol). The resulting solution was subsequently cooled to *ca.* 0 °C and a small excess of diethyl azodicarboxylate (13.92 g, 80 mmol) in THF (15 ml) was added dropwise to it from a pressure equalizing funnel. The solution was allowed to warm to room temperature and stirred at this temperature under a nitrogen atmosphere for 48 h. Subsequent removal of the THF left a brown oil which was triturated in methanol and then left overnight in the refrigerator to give crude compound (**25**) as a solid product which was filtered off. Recrystallization of this material from methanol provided (**25**) as a white crystalline solid (10.37 g, 51%), m.p. 98—100 °C; $\nu_{max.}$(KBr disc) 1 770, 1 750, 1 720, and 1 505 cm^{-1}; $\delta_H(CDCl_3)$ 3.45 (3 H, s), 3.55 (2 H, s), 3.95—4.3 (4 H, m), and 6.75—7.9 (8 H, m); $\delta_C([^2H_6]DMSO)$ 34.6, 37.1, 51.2, 64.7, 111.6., 120.6, 123.1, 128.4, 130.9, 131.6, 134.3, 156.2, 167.7, and 171.2; *m/z* 339 (M^+, 1.4%), 175 (10), 174 (100), 130 (18) (Found: C, 67.2; H, 5.2; N, 4.0%; M^+, 339.1104. $C_{19}H_{17}NO_5$ requires C, 67.2; H, 5.05; N, 4.1%; *M*, 339.1106).

2-[2′-(N-*Phthalimido*)*ethoxy*]*phenylacetic Acid* (**26**).—The reaction procedure used for the synthesis of compound (**26**) was identical with that previously described for the synthesis of compound (**9**) (yield 78%), m.p. 169—171 °C; $\nu_{max.}$ (KBr disc) 3 050 and 1 725 cm^{-1}; $\delta_H([^2H_6]DMSO)$ 3.45 (2 H, s), 3.95 (2 H, t, *J* 6 Hz), 4.15 (2 H, t, *J* 6 Hz), 6.75—7.75 (4 H, m), 7.85 (4 H, pseudo singlet), and 12.45 (1 H, br, exch.); $\delta_C([^2H_6]DMSO)$ 34.8, 36.9, 64.7, 111.5, 120.5, 123.0, 123.8, 128.1, 130.9, 131.5, 134.3, 156.1, 167.7, and 172.4; *m/z* 325 (M^+, 0.6%), 175 (11), 174 (100), 130 (21) (Found: C, 66.6; H, 4.7; N, 4.1. $C_{18}H_{15}NO_5$ requires C, 66.5; H, 4.6; N, 4.3%).

2-(2′-*Aminoethoxy*)*phenylacetic Acid* (**27**).—Hydrazine acetate was formed *in situ* by addition of hydrazine hydrate (5 ml) to ethanol (75 ml) followed by dropwise addition of glacial acetic acid until the pH of the solution reached 7. The phthalimide (**26**) (3.4 g, 10.5 mmol) was then added to the resulting solution which was refluxed for 2 h and left overnight. Most of the phthalohydrazide was precipitated and this was separated. Removal of the methanol from the filtrate left a colourless gum. The product was isolated from this gum by gradient-elution column chromatography using Kieselgel 60 silica gel and a chloroform–methanol elution system (20% MeOH rising to 100%), and was isolated as a white crystalline solid (1.3 g, 65%), m.p. 225 °C; $\nu_{max.}$ (KBr disc) 3 400—2 300br, 2 175, 1 580, and 1 295 cm^{-1}; $\delta_H(D_2O)$ 3.4 (2 H, t, *J* 5 Hz), 3.5 (2 H, s), 4.25 (2 H, t, *J* 5 Hz), and 6.9—7.45 (4 H, m) (Found: C, 61.3; H, 6.9; N, 7.1. $C_{10}H_{13}NO_3$ requires C, 61.5; H, 6.7; N, 7.2%).

Methyl 2-(2-*Aminoethoxy*)*phenylacetate Hydrochloride* (**28**).—To a stirred solution of compound (**27**) (2.00 g, 10.0 mmol) in methanol (25 ml) at 0 °C, was slowly added dropwise from a pressure equalizing funnel an excess of thionyl chloride (3.7 g, 30 mmol). The solution was allowed to warm to room temperature after which it was stirred for a further 3 h. The methanol and excess of thionyl chloride were then removed under reduced pressure to leave a solid which upon recrystallization from chloroform–acetone [10] gave crystalline compound (**28**) (1.81 g, 75%); $\nu_{max.}$ (KBr disc) 3 500, 2 100, 1 735, and 1 590

cm^{-1}; $\delta_H([^2H_6]DMSO)$ 3.1—3.7 (7 H, m), 4.1 (2 H, t, *J* 5 Hz), 6.6—7.8 (4 H, m), and 8.0—8.7 (3 H, br exch.).

N-{2-[2-(*Methoxycarbonylmethyl*)*phenoxy*]*ethyl*}-m-*hydroxyphenylacetamide* (**29**).—The reaction procedure used for the synthesis of compound (**29**) was identical with that previously described for the synthesis of compound (**16**) (yield 44%); thick gum; $\nu_{max.}$ (Nujol mull) 3 335, 1 745, 1 660, 1 600, and 1 550 cm^{-1}; $\delta_H(CDCl_3)$ 3.4—3.6 (6 H, m), 3.55 (3 H, s), 3.9 (2 H, t, *J* 5 Hz), 6.6—7.3 (9 H, m), and 8.45 (1 H, br, exch.); $\delta_C(CDCl_3)$ 36.3, 39.1, 43.2, 52.0, 66.4, 111.5, 114.4, 116.3, 120.5, 121.0, 123.0, 128.8, 130.0, 131.0, 136.2, 156.2, 157.2, 172.3, and 173.0; *m/z* 343 (M^+, 0.4%), 179 (11), 178 (100), 107 (32), and 44 (18).

N-{2-[2-(*Carboxymethyl*)*phenoxy*]*ethyl*}-m-*hydroxyphenylacetamide* (**30**).—The reaction procedure used for the synthesis of (**30**) was similar to that previously described for the synthesis of compound (**19**). Isolation of compound (**30**) was achieved in 90% yield after flash column chromatography using Kieselgel 60 silica gel and a 90% $CHCl_3$, 9% isopropyl alcohol, 1% acetic acid eluant system; thick gum; $\nu_{max.}$ (Nujol mull), 3 650—2 400, 1 710, 1 660, and 1 545 cm^{-1}; $\delta_H([^2H_6]DMSO)$ 3.2—3.7 (6 H, m), 3.95 (2 H, t, *J* 5 Hz), 6.5—7.3 (8 H, m), 8.0 (1 H, t, *J* 5 Hz, exch.), 10.2 (1 H, br, exch.), and *ca.* 12 (1 H, br, exch.); $\delta_C([^2H_6]DMSO)$ 35.4, 38.4, 42.4, 66.6, 111.8, 113.5, 116.1, 119.7, 120.5, 124.0, 128.2, 129.2, 130.9, 137.5, 156.4, 157.3, 170.7, and 173.0; *m/z* 179 (18%), 178 (100), 107 (70), 77 (21), and 44 (53).

Lactone (**2a**).—The hydroxy acid (**30**) (0.75 g, 2.28 mmol), di-2-pyridyl disulphide (0.75 g, 3.42 mmol) and triphenylphosphine (0.90 g, 3.42 mmol) were added to 1,4-dioxane (10 ml) under nitrogen and stirred at room temperature for 5 h. The resulting yellow solution containing the pyridine-2-thiol ester was diluted with xylene (15 ml) and the solution then added slowly from a mechanically driven syringe over a period of 15 h to refluxing xylene (300 ml) under nitrogen. Reflux was continued for an additional 15 h after complete injection of the thiol ester solution. Following this reflux period the xylene and dioxane were removed under reduced pressure to give a yellow oil. Isolation of the lactone from other reaction by-products was achieved by gradient-elution chromatography using Kieselgel 60 silica gel and a light petroleum–ethyl acetate elution system. The lactone isolated from the column was still slightly impure. Recrystallization from chloroform–methanol provided crystalline compound (**2a**) (0.14 g, 20%), m.p. 260—262 °C; $\nu_{max.}$ (KBr disc) 3 250, 3 090, 1 770, 1 650, and 1 575 cm^{-1}; $\delta_H([^2H_6]DMSO)$ 3.35—3.6 (4 H, m), 3.85 (2 H s), 4.05 (2 H, t, *J* 5 Hz), and 6.8—7.6 (9 H, m); *m/z* 311 (M^+, 2.0%), 178 (100), 177 (36), 107 (20.5), 78 (23.5), and 44 (32) (Found: C, 69.0; H, 5.3; N, 4.2%; M^+, 311.1157. $C_{18}H_{17}NO_4$ requires C, 69.4; H, 5.5; N, 4.5%; *M*, 311.1157).

Acknowledgements

We thank the S.E.R.C. for a C.A.S.E. Studentship (initially to P. G. O. and then to I. K. M.) and Dr. Simon Campbell for useful discussions.

References

1 For recent reviews of macrolides see K. C. Nicolaou, *Tetrahedron*, 1977, **33**, 683; W. D. Celmer, *Pure Appl. Chem.*, 1971, **28**, 413; T. G. Back, *Tetrahedron*, 1977, **33**, 3041.
2 (*a*) F. Vögtle and B. Jansen, *Tetrahedron Lett.*, 1976, 4895; (*b*) D. E. Fenton, D. Parkin, and R. F. Newton, *J. Chem. Soc., Perkin Trans. 1*, 1981, 449.
3 'Burgar's Medicinal Chemistry,' ed. M. E. Wolff, Wiley-Interscience, New York, 4th edn., 1981.
4 C. E. Malmberg and C. McGratten, *J. Pharm. Sci.*, 1975, **64**, 1240.
5 H. R. Ing and R. H. F. Manske, *J. Chem. Soc.*, 1926, 2348.
6 J. C. Sheehan and J. J. Hlavka, *J. Org. Chem.*, 1956, **21**, 439; S. Antonio and A. R. Rocha, *Circ. Res.*, 1962, **11**, 910.
7 E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, 1974, **96**, 5614.
8 S. Bittner and Y. Assaf, *Chem. Ind.*, 1975, 281; M. S. Manhas, W. H. Hoffman, B. Lal, and A. K. Bose, *J. Chem. Soc., Perkin Trans. 1*, 1975, 461; R. J. Bass, B. J. Banks, M. R. G. Leeming, and M. Snarey, *ibid.*, 1981, 124.
9 T. O. Soine and M. R. Buchdahl, *Org. Synth.*, Coll. Vol. IV, p. 107.

Received 2nd *December* 1986; *Paper* 6/2323