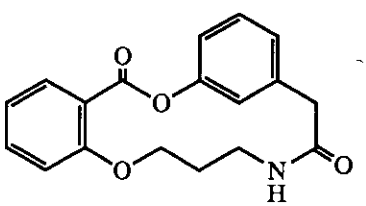
SYNTHESIS OF A NOVEL MACROCYCLIC LACTONE SYSTEM†

Keith Smith* and Ian K Morris
Department of Chemistry, University College of Swansea,
Singleton Park, Swansea SA2 8PP, U.K.

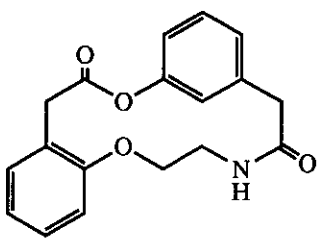
Robert J. Bass
Pfizer Central Research, Sandwich, Kent, CT13 9NJ, U.K.

Abstract - A total synthesis of a 14-membered ring lactone (**3**) with potential biological activity is described. The final lactonization step uses a modification of the Corey pyridinethiol ester procedure.

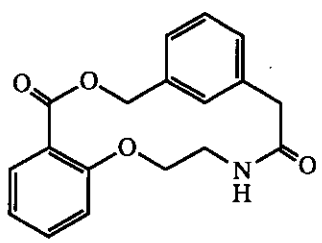
We have previously reported the syntheses of novel macrocyclic lactone systems (**1**) and (**2**).[1] As part of the same study we also wished to have access to the related lactone-lactam system (**3**), which has CH_2 and CO_2 units transposed with respect to **2**, for comparison. We now report the successful synthesis of the novel macrocyclic system.



(1)



(2)

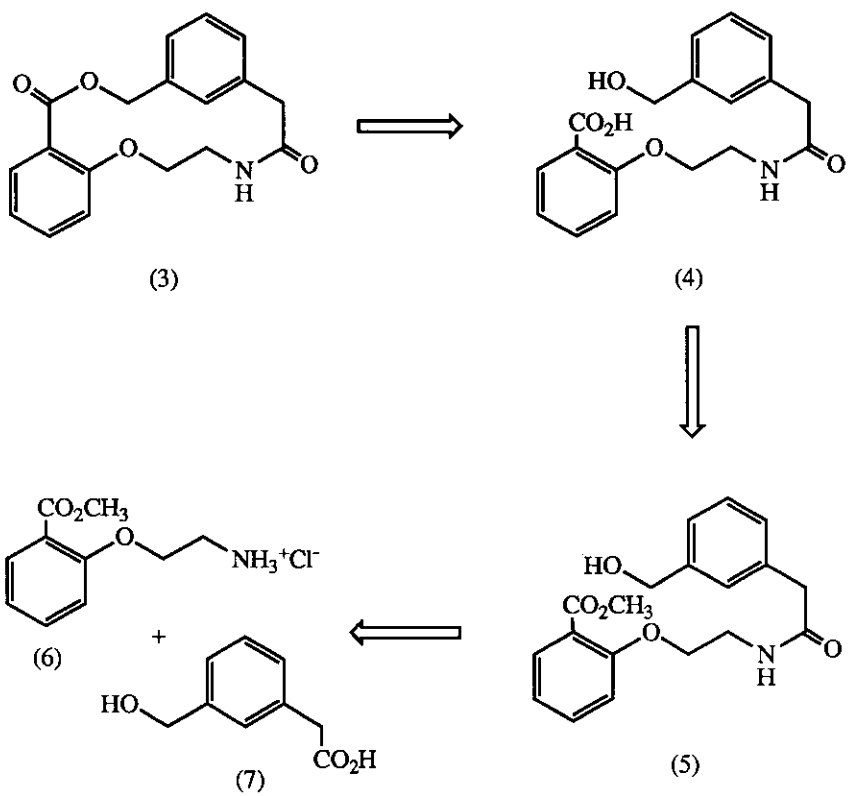


(3)

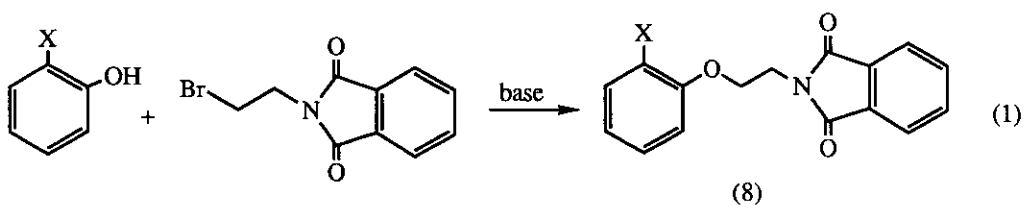
† Dedicated to Professor Alan Katritzky on the occasion of his 65th birthday.

A retrosynthetic analysis of compound (**3**) suggested the route shown in Scheme 1. Thus, the initial synthetic targets were compounds (**6**) and (**7**).

Scheme 1



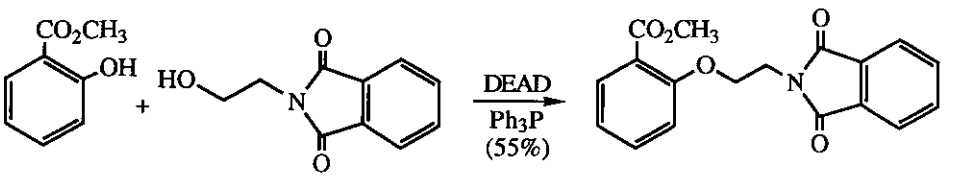
Initial attempts to synthesize **6** *via* a Williamson ether synthesis of the phthalimide (**8**) (X = CO_2CH_3) according to equation (1) met with failure, although comparable reactions gave low yields (10% and 25%, respectively) of the analogous products (**8**) (X = $COCH_3$ and CN) when applied to the appropriate starting materials.



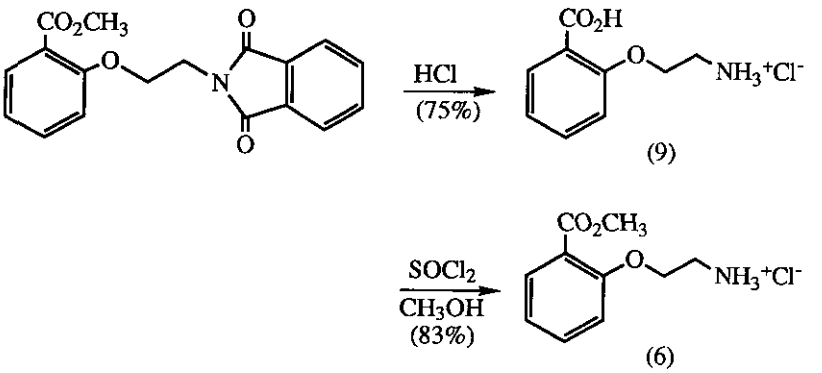
(1)

Fortunately, however, **8** (X = CO_2CH_3) was readily synthesized by coupling methyl salicylate and *N*-(2-hydroxyethyl)phthalimide with the aid of diethyl azodicarboxylate (DEAD), as in equation (2).[2] This

phthalimide was readily hydrolysed with concomitant hydrolysis of the ester function, using 36% hydrochloric acid under reflux conditions. The resulting amino acid (**9**) was then re-esterified using thionyl chloride in methanol to give the initial target compound (**6**) in high yield (equation 3).



(2)

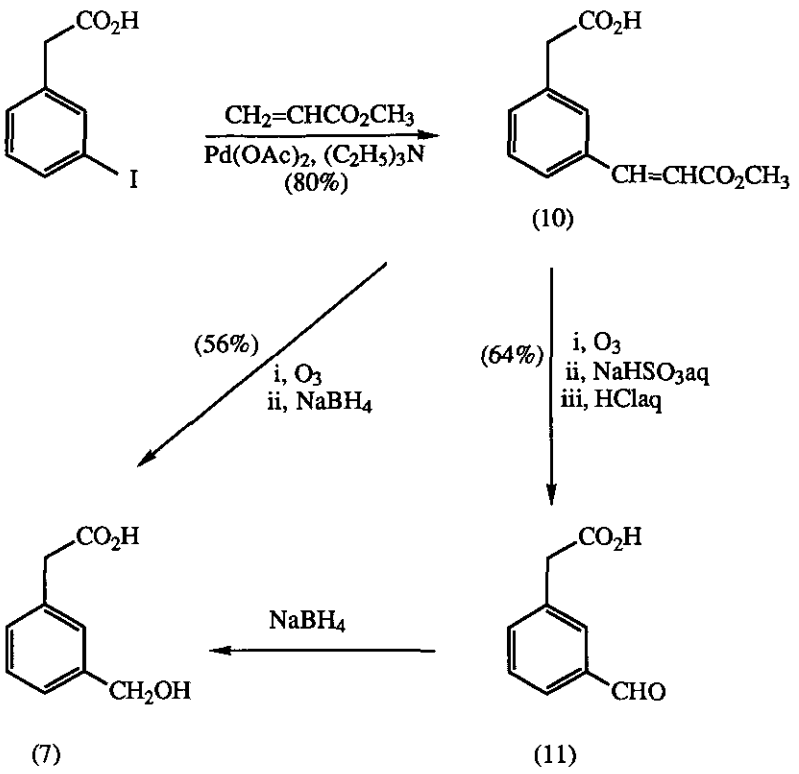


(3)

Scheme 2 shows the approach utilised for the synthesis of 3-hydroxymethylphenylacetic acid (**7**). A palladium catalysed coupling reaction[3] of 3-iodophenylacetic acid with methyl acrylate to give compound (**10**) and subsequent ozonolysis of the double bond gave 3-formylphenylacetic acid (**11**). Compound (**11**) was readily reduced to **7** using sodium tetrahydroborate, but the sequence of ozonolysis and reduction could be carried out without prior isolation of **11**, providing an improved overall yield for the conversion of **10** into **7**.

Coupling of compound (**6**) with (**7**) was achieved with the aid of the water soluble carbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, to give the amide (**5**) (see Scheme 1) in 68% yield. Mild base hydrolysis cleaved the ester to provide the seco-acid (**4**) in 80% yield and this was subsequently cyclized to the target lactone (**3**) using our modification of the Corey pyridinethiol ester double activation method[4] which had proved successful in our earlier syntheses of lactones (**1**) and (**2**).[1] The availability of lactone-lactams (**1-3**) allows the possibility of comparing the effects of different structural features on the biological activity of these potential phenylethylamine analogues.

Scheme 2



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 tlc was performed using Merck silica gel 60 F254 precoated sheets (0.2mm). Proton nmr spectra were obtained on a Varian HA 100 or XL100 spectrometer with tetramethylsilane as an internal standard. Carbon-13 nmr spectra were obtained on a Varian XL-100 spectrometer. Infra-red 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 admixtures. Mass spectra were measured using a modified Kratos MS9 instrument under electron impact conditions.

Methyl [2-(2-*N*-phthalimido)ethoxy]benzoate (8, X = CO_2CH_3)

To *N*-(2-hydroxyethyl)phthalimide (15.28 g, 80 mmol) and methyl salicylate (12.16 g, 80 mmol) in THF (150 ml) under nitrogen was added triphenylphosphine (23.58 g, 90 mmol). The resulting solution was subsequently cooled to around 0°C (ice bath) and diethyl azodicarboxylate (15.66 g, 90 mmol) in THF

(10 ml) added dropwise over 4 h. The solution was allowed to warm to ambient temperature and stirred under nitrogen for 48 h. Subsequent removal of the THF left a brown oil which upon trituration in methanol and overnight standing in the refrigerator gave crude (**8**, X = CO_2CH_3) as a solid product which was isolated by filtration. Recrystallisation from methanol provided a white crystalline solid (14.2 g, 55%). Further product was obtainable by silica gel chromatography of the mother liquors. mp 108-109°C; ν_{max}(KBr) = 1775, 1725, 1600 cm^{-1}; ^1H nmr, $\delta_H(CDCl_3)$ = 3.75 (3H, s), 4.0-4.35 (4H, m), 6.8-7.0 (2H, m), 7.25-7.85 (6H, m); ^{13}C nmr, $\delta_C(CDCl_3)$ = 37.1, 52.0, 65.4, 113.5, 120.8, 121.1, 123.2, 131.6, 132.1, 133.2, 133.9, 157.4, 166.9, 168.0; ms; m/z (relative intensity) = 325 (M^+, 0.6%), 173 (100). Anal. Calcd for $C_{18}H_{15}NO_5$: C, 66.45; H 4.65; N, 4.3. Found: C, 66.3; H, 4.7; N, 4.5.

2-[2-(*N*-Phthalimido)ethoxy]acetophenone (8, X = $COCH_3$)

N-(2-Bromoethyl)phthalimide (2.54 g, 10 mmol) and 2'-hydroxyacetophenone (1.36 g, 10 mmol), together with a large excess of dry potassium carbonate (5 g), were refluxed in dry acetone (50 ml), whilst being vigorously stirred for a period of 24 h. Removal of the acetone under reduced pressure resulted in an off-white solid. Chloroform was added in order to dissolve the organic material and the residual suspension was removed by filtration. Evaporation of the chloroform produced a white solid which was chromatographed using Kieselgel 60 silica gel and eluted with a mixture of petroleum ether and ethyl acetate (50:50), producing starting components and the product **8** (X = $COCH_3$) which was recrystallised from methanol (0.31g, 10%). mp 168-169°C; ν_{max}(KBr) = 1780, 1735, 1675, 1600 cm^{-1}; ^1H nmr, δ_H (DMSO-d_6) = 2.35 (3H, s), 4.0 (2H, t, J = 5 Hz), 4.3 (2H, t, J = 5 Hz), 6.75-7.9 (8H, m); ms; m/z (relative intensity) = 309 (M^+, 1.7%), 174 (100).

2-[2-(*N*-Phthalimido)ethoxy]benzonitrile (8, X = CN)

The preparation of (**8**, X = CN) was carried out in a manner similar to that of (**8**, X = $COCH_3$). Yield 25%; mp 148-149°C; ν_{max}(KBr) = 2240, 1775, 1715 cm^{-1}; ^1H nmr, δ_H ($CDCl_3$) = 4.0-4.5 (4H, m), 6.8-7.0 (8H, m); ^{13}C nmr, $\delta_C(CDCl_3)$ = 36.6, 65.2, 102.4, 112.4, 115.9, 121.3, 123.4, 131.9, 133.8, 134.1, 134.3, 159.7, 167.9; ms; m/z (relative intensity) = 292 (M^+, 18.4%), 174 (100). Anal. Calcd for $C_{17}H_{12}N_2O_3$: C, 69.85; H, 4.15; N, 9.6. Found: C, 70.1; H, 4.1; N, 9.6%.

2-(2-Aminoethoxy)benzoic acid hydrochloride (9)

Compound (**8**, X = CO_2Me) (4.63 g, 15 mmol) was dissolved in 1,4-dioxane (25 ml) and an equivalent volume of concentrated 36% hydrochloric acid. This solution was then heated at reflux for 48 h. The 1,4-dioxane and hydrochloric acid were both removed under reduced pressure to give a colorless gum which was triturated with acetone to leave a white precipitate which was isolated by filtration. Recrystallisation from acetone/methanol provided (**9**) (2.45 g, 75%); mp 179-182°C; ν_{max}(KBr) = 3290, 3000 (br), 1710, 1600 cm^{-1}; ^1H nmr, δ_H (DMSO-d_6) = 3.1 (2H, t, J = 5 Hz), 4.35 (2H, t, J = 5 Hz), 6.9-7.65 (3H, m), 7.7 (1H, dd, J = 1.5 Hz and 8 Hz), 7.9-9.2 (4H, broad, exch.); ms; m/z (relative intensity) = 181 (M^+ -HCl, 0.4%).

Methyl 2-(2-aminoethoxy)benzoate hydrochloride (6)

To a stirred solution of (**9**) (2.65 g, 12 mmol) in methanol (75 ml), cooled to 0°C (ice bath), was slowly added dropwise, excess thionyl chloride (4.76 g, 40 mmol). The resulting solution was then warmed to 40°C and stirred for a further 10 h. Upon reaction completion, the methanol and excess thionyl chloride were removed under reduced pressure to give an off-white solid. Recrystallisation from chloroform/acetone produced (**6**) (1.92 g, 83%); mp 127-128°C; ν_{max}(KBr) = 3100-2500 (br), 2050, 1700, 1605 cm^{-1}; ^{1}H nmr, $\delta_H(CDCl_3)$ = 3.45 (2H, t, J = 5 Hz), 3.8 (3H, s), 4.4 (2H, t, J = 5 Hz), 6.85-7.1 (2H, m), 7.3-7.55 (1H, m), 7.75 (1H, dd, J = 1.5 and 8 Hz), 8.2-9.2 (3H, br, exch.); ^{13}C nmr, $\delta_C(CDCl_3)$ = 39.8, 52.5, 66.2, 115.8, 120.3, 122.0, 131.7, 134.3, 158.0, 166.7.

[3-(3-Methoxy-3-oxo-1-propenyl)phenyl]acetic acid (10)

3-Iodophenylacetic acid (0.734 g, 2.8 mmol), methyl acrylate (0.409 g, 4.75 mmol), triethylamine (0.385 g, 3.8 mmol) and anhydrous palladium acetate (0.006 g, 1 mol %) were dissolved in acetonitrile (5 ml) and stirred at 100°C under an inert atmosphere for a period of 10 h. The acetonitrile and excess methyl acrylate were removed under reduced pressure, leaving a dark oil. To this oil was added 2 molar hydrochloric acid (15 ml) and the organic products were then extracted with ethyl acetate (3 x 15 ml). The extracts were combined, dried ($MgSO_4$) and the ethyl acetate was removed to give a brown solid material. Recrystallisation of this material from chloroform and ethyl acetate gave (**10**) as a white crystalline solid (0.493 g, 80%); mp 119-121°C; ν_{max}(KBr) = 3000 (br), 1710, 1640 cm^{-1}; ^{1}H nmr, δ_H (DMSO-d_6) = 3.6 (2H, s), 3.7 (3H, s), 6.575 (1H, d, J = 16 Hz), 7.7-7.75 (5H, m), 12.3 (1H, broad, exch.); ms; m/z (relative intensity) = 220 (M^+, 29.3%), 143 (100).

(3-Formylphenyl)acetic acid (11)

Into a stirred solution of (**10**) (0.22 g, 1.0 mmol) in ethyl acetate (50 ml), cooled to –78°C, was bubbled a stream of ozonised oxygen, until an aliquot test portion of the solution no longer decolorised a dilute bromine solution, thus avoiding over oxidation. When the reaction was complete, reduction of the ozonide was achieved by vigorous shaking of the ethyl acetate solution with an aqueous solution of sodium sulfite. The aqueous layer was acidified to pH 1 using 3 molar hydrochloric acid and the organic layer was separated after further shaking. The aqueous layer was washed with further aliquots of ethyl acetate (2 x 50 ml), the organic extracts were combined and dried ($MgSO_4$) and the ethyl acetate was removed to leave a crude white solid. This material was chromatographed using Kiesel gel 60 silica gel and eluted with 90% chloroform 9% propan-2-ol - 1% acetic acid to give (**11**) (0.105 g, 64%); mp 96-97°C; ν_{max}(KBr) = 2950, 1710 cm^{-1}; ^{1}H nmr, $\delta_H(CDCl_3)$ = 3.7 (2H, s), 7.2-7.85 (4H, m), 9.95 (1H, s), 10.5-11.0 (1H, br, exch.); ms; m/z (relative intensity) = 164 (M^+, 71%), 119 (100). This compound has previously been reported in the patent literature.[5]

***3-Hydroxymethylphenylacetic acid*(7) directly from 10 without isolation of 11**

Into a stirred solution of (**10**), (2.20 g, 10 mmol) in methanol (125 ml), cooled to –5°C, was bubbled a stream of ozonised oxygen, until an aliquot test portion of the solution no longer decolorised a dilute bromine

solution. The resulting ozonide solution was then added dropwise to an ice-cold solution of sodium tetrahydroborate (1.13 g, 30 mmol) and sodium hydroxide (0.60 g, 15 mmol) in 50% aqueous ethanol (75 ml). A gentle evolution of hydrogen resulted and stirring was continued at room temperature for 15 h. The solution was concentrated by removal of the methanol and ethanol and the resulting aqueous solution was acidified to pH 1 by dropwise addition of ice-cold 3 molar hydrochloric acid. The precipitated material was extracted into ethyl acetate and isolated by column chromatography using Kiesel gel 60 eluted with 90% chloroform - 9% propan-2-ol - 1% acetic acid to give (**7**), (0.93 g, 56%); mp 98-99°C. ν_{max}(KBr) = 3325, 2950 (br), 1695 cm^{-1}; ^1H nmr, δ_H (DMSO-d_6) = 3.5 (2H, s), 4.5 (2H, s), 7.9-8.4 (4H, m - the exchangeable protons were not observed); ^{13}C nmr, δ_C(DMSO-d_6) = 40.8, 62.8, 124.7, 127.3, 127.6, 117.9, 134.7, 148.5, 172.7; ms; m/z (relative intensity) = 166 (M^+, 40%), 91 (100). Anal. Calcd for $C_9H_{10}O_3$: C, 65.0; H, 6.1. Found: C, 65.0; H, 6.1.

***N*-[2-[2-Methoxycarbonylphenoxy]ethyl]-2-[3-hydroxymethylphenyl]acetamide (5)**

Compounds (**6**) (3.47 g, 15 mmol) and (**7**) (2.49 g, 15 mmol), together with a small excess of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.44 g, 18 mmol) and triethylamine (1.82 g, 18 mmol), were added to a mixture of acetonitrile and tetrahydrofuran (1:1; 75 ml). The resulting solution was stirred under nitrogen at ambient temperature for 24 h. The insoluble triethylammonium chloride which precipitated was removed by filtration and the filtrate was evaporated to dryness. The resulting oil was dissolved in chloroform (50 ml), washed successively with 3 molar hydrochloric acid (50 ml), 10% sodium bicarbonate (50 ml) and water (50 ml), then dried ($MgSO_4$). Removal of the chloroform left a light brown oil which was chromatographed using Kiesel gel 60 and eluted with 98% chloroform:2% methanol. This produced (**5**) (3.50 g, 68%) as a thick translucent gum which would not crystallise; ν_{max}(neat) = 3350 (br), 1725, 1665 cm^{-1}; ^1H nmr, δ_H($CDCl_3$) = 3.35-3.65 (5H, m), 3.75 (3H, s), 4.0 (2H, t, J = 5 Hz), 4.5 (2H, s), 6.8-7.45 (8H, m), 7.75 (1H, dd, J = 2 and 8 Hz); ms; m/z (relative intensity) 343 (M^+, 2.4%), 192 (100).

***N*-[2-[2-Carboxyphenoxy]ethyl]-2-[3-hydroxymethylphenyl]acetamide (4)**

To (**5**) (0.686 g, 2.0 mmol) was added a three molar excess of aqueous sodium hydroxide solution (240 mg in 10 ml). The compound completely dissolved following several minutes stirring at ambient temperature. Monitoring of the reaction by tlc (90% dichloromethane:9% propan-2-ol:1% AcOH) showed complete hydrolysis of the ester to the carboxylate salt after 5 h. The solution was then acidified with 3 molar of hydrochloric acid and the organic products were extracted into chloroform, dried ($MgSO_4$) and concentrated to leave a light brown oil. Chromatography, using Kiesel gel 60 and 90% chloroform:9% propan-2-ol:1% AcOH as eluant produced (**4**) as a thick translucent gum which did not crystallise (0.526 g, 80%); ν_{max}(neat) = 3320 (br), 1725, 1655 cm^{-1}; ^1H nmr, δ_H($CDCl_3$) = 3.2-3.65 (4H, m), 4.0 (2H, t, J = 5 Hz), 4.5 (2H, s), 6.75-8.6 (10H, m), 8.85 (1H, dd, J = 1.5 and 7 Hz); ^{13}C nmr, δ_C($CDCl_3$) = 39.0, 43.2, 64.4, 68.2, 113.9, 119.5, 121.4, 126.0, 128.1, 128.3, 128.8, 132.6, 134.3, 134.9, 141.3, 158.1, 167.8, 172.6; ms; m/z (relative intensity) = 329 (M^+, 7.7%), 192 (74), 190 (91), 121 (100), 120 (97).

Target Lactone (3)

The hydroxyacid (**4**) (0.822 g, 2.50 mmol) and 2,2′-dipyridyl disulfide (Aldrithiol-2) (0.826 g, 3.75 mmol) were dissolved in 1,4-dioxane (10 ml) and stirred under nitrogen at room temperature for 5 h. The resulting yellow solution containing the 2-pyridinethiol ester was diluted with xylene (15 ml)[6] and then slowly added from a mechanically driven syringe over a period of 25 h to xylene (100 ml) at reflux temperature under a nitrogen atmosphere. Reflux was continued for an additional 15 h after complete addition of the thiol ester. Subsequent removal of the xylene and dioxane under reduced pressure gave an orange gum. Trituration of this gum with ethyl acetate provided the lactone in a crude solid form which was isolated by filtration. Recrystallisation of this material from tetrahydrofuran gave the desired lactone (139 mg, 18%), mp 260-262°C; ν_{max}(KBr) = 3190, 3100, 1745, 1650 cm^{-1}; ^1H nmr, δ_H(DMSO-d_6) = 3.43 (2H, s), 3.45 (2H, q, J = 5 Hz), 4.25 (2H, t, J = 5 Hz), 5.45 (2H, s), 6.98-7.65 (8H, m), 8.25 (1H, t, J = 7 Hz); ms; m/z (relative intensity) = 311 (M^+, 9.7%), 104 (100); accurate mass, calcd for $C_{18}H_{17}NO_4$ = 311.1157; found = 311.1156. Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.4; H, 5.5; N, 4.5. Found: C, 69.1; H, 5.7; N, 4.4.

ACKNOWLEDGEMENT

We thank the SERC for a CASE studentship (to IKM).

REFERENCES AND NOTES

1. K. Smith, I.K. Morris, P.G. Owen, and R.J. Bass, *J.Chem.Soc., Perkin Trans. 1*, 1988, 77.
2. S. Bittner and Y. Assaf, *Chem.Ind. (London)*, 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.
3. R.F. Heck and J.P. Nolley, *J.Org.Chem.*, 1972, **37**, 2320.
4. E.J. Corey and K.C. Nicolaou, *J.Am.Chem.Soc.*, 1974, **96**, 5614.
5. E.M. Schultz, U.S. Patent 3,860,639 (1975) (*Chem.Abstr.*, 1975, **82**, 139707x).
6. The procedure is analogous to that developed for the preparation of lactones (**1**) and (**2**) - see ref. 1.

Received, 1st December, 1993