SYNTHESIS OF 32 - CROWN - 8 TETRAESTER COMPOUND : MODEL OF MACROTETROLID ANTIBIOTICS

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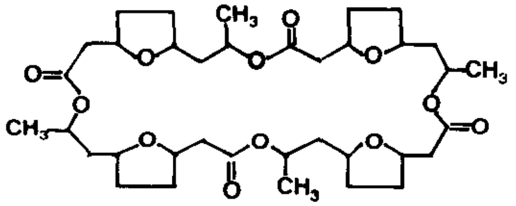
Abstract - A simple synthesis of a new thirty two membered macrocycle including height oxygen atoms (four ether, four esters) is described. This compound is a structural model of macrotetrolid nactins (ionophorous natural antibiotics)

The macrotetrolide nactins are ionophorous antibiotics[1]. From a structural point of view they are macrocycles with thirty two links including four ether functions (furan) and four esters ones (1 = monactin). The total synthesis of these compounds is long and uneasy[2-3]. Our aim is the synthesis of simple and easily attainable models of these natural compounds. In a previous communication[4], we pointed out the obtention of a macrocycle having their main characteristics, but in which the ether and ester functions had a different arrangement. We present here the synthesis of a new model, more alike natural compounds (2). This synthesis requires methods relatively easy to make use of (cf. scheme II). Scheme I represents the obtaining of intermediary products. The original compounds : 3,3' -oxidipropionitril and 3,3'-oxidipropionic acid are described [5-6]. Because of some difficulties to prepare the diacid in a reproductible manner we brought some modifications to the operating method. The hydrolysis of dinitrile under mild conditions of temperature leads to the expected product with a good efficiency, whereas under usual conditions 15 to 20 % of secondary products are formed which made the purification very delicate[7] (probably the result of the breaking of carbon oxygen ether bond : NMR data indicates the presence of an ester type methylene group). The bromo alcohol 6 can be obtained through reduction of the corresponding bromo-ketone 5, itself



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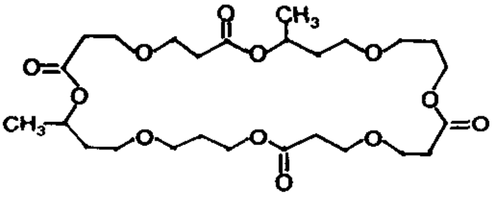

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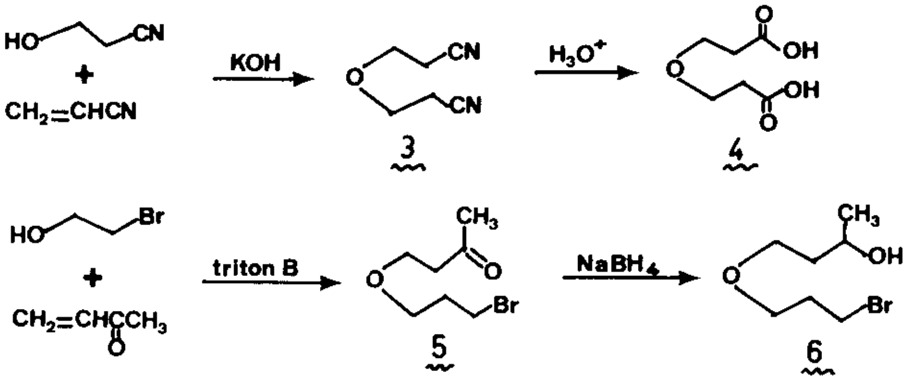
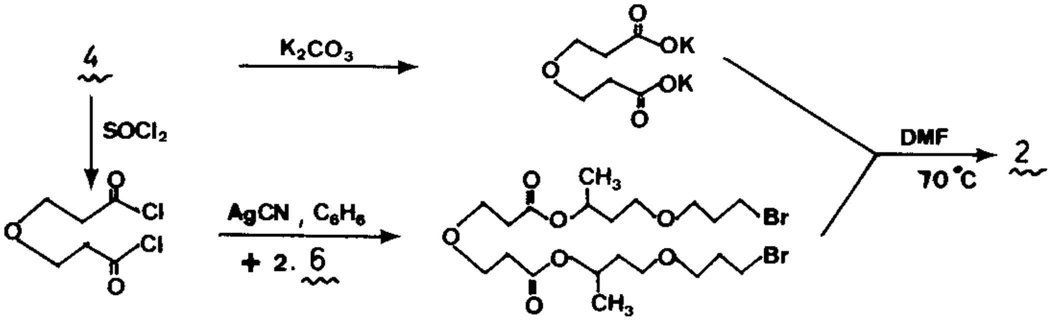


Scheme I

obtained with good yield by addition of 3-bromo-1-propanol on methyl vinyl ketone.

The preparation of diester 7 by condensation of diacid chloride upon alcohol in pyridin can be made with an average yield. We prefered S. TAKIMOTO'S method which enable the obtaining of esters



Scheme II

from hindered alcohols with good yields[8]. At the final stage of cyclisation, the main difficulty lies in the purification of the macrocycle. This one is obtained from chromatography on silica gel followed by successive extractions with pentane. Nevertheless, we can point out that the overall yield is good for a cycle of this size.

Experimental results for new compounds are collected in the following table. Operating methods are also described.

3,3' - Oxydipropionic acid 4 : To 3,3' -oxydipropionitrile [5] (24.8 g, 0.2 mol.), 65 ml of aqueous acid chloride (d = 1.18) are added. The mixture is stirred at 50° C for 24 h, and at room temperature for 12 h. The mixture is concentrated under reduced pressure. 300 ml of diethyl ether are added, and the precipitate of ammonium chloride is filtered off. The solution is dried with magnesium sulfate. Evaporation under reduced pressure gives 24.4 of the title product which cristallizes on standing. Yield : 75 % ; m.p. 60° C (from petroleum ether / diethyl ether) ; lit. (6-7) m.p. 60-61° C.

Compound	bp(°C)	Yield (%)	Microanalysis(a)		^{1}H and ^{13}C N M R Spectra(b)
			C	H	
2 (c)	oil	25	56.92 56.68	8.08 8.02	1.25 (d, 6H); 1.90 (m, 8H); 2.52 (t, 4H); 2.55 (t, 4H); 3.45 (t large 8H); 3.72 (t, 8H); 4.15 (t, 4H); 5.02 (sex, 2H) 19.9 (two $-CH_3$); 28.6 (two $-OCH_2\underline{C}H_2CH_2O-$); 34.6 (two $-OCHCH_3\underline{C}H_2CH_2-$); 34.9 and 35.5 (two $-OCH_2\underline{C}H_2COOCHCH_3-$ and two $-OCH_2\underline{C}H_2COOCH_2-$); 61.4 (two $-OCOO\underline{C}H_2-$); 66.0 (four $-O\underline{C}H_2CH_2COO$); 66.8 (four $-O\underline{C}H_2CH_2CH_2OOC$);68.3(two $-COO\underline{C}HCH_3-$) 170.6 and 171.0 (two + two -CO-).
5	84-86/ 0.05 mm	70	40.21 40.31	6.27 6.03	2.05 (quint., 2H); 2.17 (s, 3H); 2.65 (t, 2H); 3.45 (t 2H); 3.52 (t, 2H); 3.70 (t, 2H). 30.2 ($-CH_3$); 32.8 ($-OCH_2\underline{C}H_2CH_2Br$); 30.6 ($-\underline{C}H_2Br$); 43.6 ($-\underline{C}H_2CO-$); 65.9 ($-O\underline{C}H_2CH_2CO-$); 68.2 ($-O\underline{C}H_2CH_2CH_2Br$); 206.2 (-CO-).
6	85-90/ 0.02 mm	82	39.90 40.01	7.25 7.12	1.10 (d, 3H); 1.70 (d of d, 2H); 2.08 (quint, 2H); 3.05 (S, 1H); 3.47 (t, 2H); 3.55 (t, 2H); 3.60 (t, 2H); 3.95 (sex, 1H). 23.5 ($-\underline{C}H_3$); 32.9 ($-OCH_2\underline{C}H_2CH_2Br$); 30.3 ($-\underline{C}H_2Br$); 38.6 ($OCH_2\underline{C}H_2CHOH-$); 65.6 ($-\underline{C}HOH-$); 68.3 and 68.7 ($-\underline{C}H_2O\underline{C}H_2-$).
7	215-225(d)/ 0.05 mm	88	43.81 43.76	6.62 6.59	1.24 (d, 6H); 1.85 (quint, 4H); 2.10 (quad, 4H); 2.52 (t, 4H); 3.25 à 3.90 (4t, 16H); 5.05 (sex, 2H). 20.3 (two $-\underline{C}H_3$); 30.5(two $-\underline{C}H_2Br$); 32.9 (two $-OCH_2\underline{C}H_2CH_2Br$); 35.4 and 36.0 (two $-OCH_2\underline{C}H_2CO-$ and two $-OCHOH\underline{C}H_2CH_2O-$) 66.5, 67.2, 68.2, 68.4 (two $-O\underline{C}H_2CH_2COOCHCH_3$, two $-O\underline{C}HCH_3-$, two $-O\underline{C}H_2CH_2-$, two $-O\underline{C}H_2CH_2CH_2Br$); 170.8 (two -CO-).

(a) First line : calculated values ; second line : experimental values. (b) δ ppm/TMS, solvent: $CDCl_3$
(c) For the macrocycle , mass spectroscopy analysis (NH_3 ionization) : 548 (M^+).(d) begening of decomp.

4 - (3-bromopropoxy)-2-butanone 5 : A mixture of 3-bromo-1-propanol (30 g, 0.216 mol.) and 1.8 ml of a 40 % methanolic solution of triton B is stirred for 10 min at room temperature. (Note : 3-bromo-1-propanol is stored at cool temperature and treated with sodium carbonate to prevent acidic impurities). Methyl vinyl ketone (16.6 g, 0.237 mol.) is added dropwise at such a rate that the temperature reaction is maintained to 15-20° C. The mixture is stirred at this temperature for 2 h, and then diluted with methylene chloride (100 ml), washed with water (2 x 50 ml), and dried with magnesium sulfate. The solvent is evaporated and the residue distilled.

4 - (3-bromopropoxy)-2-butanol 6 : The bromo ketone 5 (25.5 g, 0.121 mol.) is dissolved in 100 ml of methanol. The solution is cooled to -10° C and sodium borohydride (3.5 g, 0.0925 mol.) is added in portions. Stirring is continued for 1 h at room temperature. The unused hydride is destroyed by addition of dilute hydrochloric acid after cooling. The reaction mixture is poured into 600 ml of

saturated aqueous sodium chloride solution and the product extracted with diethyl ether (3 x 300 ml). The ether solution is dried with anhydrous magnesium sulfate, and after removal of the solvent, the residual product is distilled under reduced pressure.

3,3' - oxidipropionic acid 4-(3-bromopropoxy-2-butyl diester 7 : A mixture of diacid 4 (3,3 g, 0.0203 mol.) and 15 ml of thionyl chloride is stirred at 60° C for 1.5 h. Thionyl chloride is evaporated under reduced pressure and the acid dichloride is used as such for esterification. For the next manipulations, reaction flask is placed under nitrogen atmospher. To a mixture of bromo alcohol 6 (7.8 g, 0.037 mol.), silver cyanide (5 g. 0.037 mol.) and 10 ml of anhydrous benzene, a solution of the acid dichloride primarly prepared in 30 ml of anhydrous benzene is added dropwise during about 1 h (temperature : 20-25° C). The reaction mixture is stirred at 25° C for 24 h. The precipitate is filtered off, the solution diluted with 100 ml of benzene, washed with a sodium bicarbonate solution (10 % in water) and with water, dried on anhydrous magnesium sulfate. Evaporation of the solvent gives the diester. The crude product (95 % purity) can be used for the final stage. An analytical sample is prepared by chromatography on a neutral alumina column with chloroform as eluent.

32 - crown-8 tetraester 2 : A potassium carbonate solution (20 % in water) is added to a solution of diacid 4 (1.72 g, 0.0106 mol.) in 10 ml of ethyl alcohol till pH 7 is reached. The solvents are evaporated and the potassium dicarboxylate is dried under reduced pressure. The dibromoester (5.8 g, 0.0106 mol.) is added with 200 ml of anhydrous dimethylformamid. The reaction mixture is stirred for 18 h at 70° C (apparatus under nitrogen atmosphere). After removal of the solvent, 100 ml of chloroform are added and the precipitate filtered off. The chloroform solution is washed with water (2 x 30 ml), dried on anhydrous magnesium sulfate and concentrated under reduced pressure. This gave an oily residue which, after chromatography over silica gel (eluent : acetone) and several extractions with pentane at room temperature, gave the pure macrocycle 2. Yield : 1.3 g (25 %).

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Received, 29th September, 1981