Simple and High Yield Synthesis of Macrocyclic Lactones by Ring-closure of Caesium Salts of ω-Halogenoaliphatic Acids

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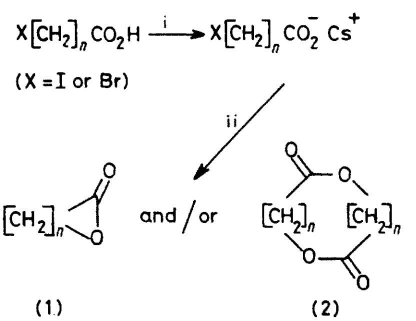
Summary A series of cyclic ketones has been subjected to Baeyer–Villiger oxidation, the derived lactone rings have been opened with hydroiodic acid, and the resulting ω-iodo-acids have been converted into their caesium salts, which re-close smoothly providing especially good yields of the larger ring macrocyclic lactones (macrolides).

CAESIUM salts[1] of aromatic dicarboxylic acids and of dihydric phenols react with dihalogenopolyethylene glycols to give crown ethers in remarkably good yields.[2,3] An analogous approach has been used for the synthesis of chiral crown ethers in which amino acids have been built into the ring.[4] It is possible that in these reactions caesium–

heteroatom interactions form the basis for a 'template effect'.[5] Therefore, we did not think that the caesium salts of ω-halogenoaliphatic acids would react intramolecularly to give lactones, particularly under our simple experimental conditions (neither high dilution nor slow addition). (The ring-closures of the alkali metal salts of ω-bromoaliphatic acids under high dilution conditions are well known.)[6,7] Contrary to our doubts, the caesium salts of ω-halogeno (chiefly iodo) aliphatic acids close smoothly to give lactones or their dimers (depending on ring size) under exceptionally mild conditions (Scheme 1).



SCHEME 1. i, Cs_2CO_3, DMF; ii, DMF, 40 °C.

The yields of the products (Table) compare favourably with those obtained using newly developed methods for macrolide synthesis.[8]

TABLE

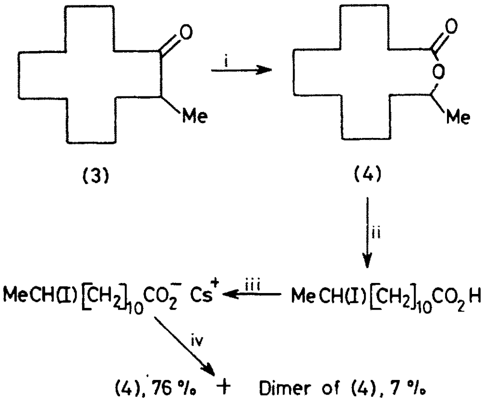
ω-Halogeno-aliphatic acid	Yield[a]/% Macrolide (**1**)	Dilide (**2**)
$I[CH_2]_4CO_2H$	$n = 4$, 70	$n = 4$[b]
$Br[CH_2]_5CO_2H$	$n = 5$[c]	$n = 5$, 88
$Br[CH_2]_8CO_2H$	$n = 8$[c]	$n = 8$, 95
$I[CH_2]_9CO_2H$	$n = 9$, 23	$n = 9$, 55
$I[CH_2]_{10}CO_2H$	$n = 10$, 33	$n = 10$, 54
$I[CH_2]_{11}CO_2H$	$n = 11$, 62	$n = 11$, 30
$I[CH_2]_{12}CO_2H$	$n = 12$, 77	$n = 12$, 18
$I[CH_2]_{13}CO_2H$	$n = 13$, 72	$n = 13$, 13
$I[CH_2]_{14}CO_2H$	$n = 14$, 83	$n = 14$, 17
$I[CH_2]_{15}CO_2H$	$n = 15$, 85	$n = 15$, 15

[a] Combined g.l.c.–^1H n.m.r. analysis; all compounds reported in the Table are known. [b] Contains only small amounts of dilide and trilide judging from g.l.c. and mass spectrum. [c] Monomer was not detected.

There is clearly a competition between the macrolide (**1**) and the dilide (**2**) formation (mass spectra reveal small amounts of trilides and tetralides; these are not detected by other techniques). The exclusive formation of a six-membered ring (**1**; $n = 4$) is not surprising[7] but the sharp changeover to exclusive formation of the dilides (**2**; $n = 5$ and 8) was not anticipated. With increasing length of the polymethylene chain there is a smooth transition from dilide to macrolide formation with the latter predominating strongly for the larger rings.

A typical experimental procedure, for the synthesis of the hexadecanolide (**1**; $n = 15$), is described below. To 16-iodohexadecanoic acid [0·5 mmol dry dimethylformamide (DMF)] is added 1 equiv. of dry Cs_2CO_3. The reaction mixture is kept at 40 °C for 24 h during which time all the Cs_2CO_3 is consumed.† Removal of the DMF followed by addition of a saturated NaCl solution and extraction with CH_2Cl_2 gives, in quantitative yield, a mixture of the hexadecanolide (**1**; $n = 15$, 85%) and the dilide (**2**; n = 15, 15%) which are separated by preparative layer chromatography on silica gel [Et_2O–light petroleum (b.p. 40—60 °C), 1:9]. The experiments leading to (**1**; $n = 4$) and (**2**; $n = 5$ and 8) were carried out at the higher concentration of 1 mmol of the acid in 25 ml of DMF. Somewhat higher yields of the dilides were obtained for reactions carried out under these conditions (Table). However, a systematic investigation of the effect of concentration on the yields of the products has not been carried out, nor have the yields reported in the Table been optimized. In our hands other alkali metal salts, using the simple conditions reported here, gave very poor yields of macrolides.

Those ω-halogenoaliphatic acids, which were not available commercially, were prepared by Baeyer–Villiger oxidation of the respective macrocyclic ketones [*m*-chloroperbenzoic acid (MCPBA) (excess), refluxing $CHCl_3$] followed by ring-opening of the lactones with HI–$MeCO_2H$ at 100 °C.[9]‡



SCHEME 2. i, MCPBA; ii, HI—$MeCO_2H$; iii, Cs_2CO_3, DMF; iv, DMF, 40 °C.

The method for macrolide synthesis reported here involves formation of a new oxygen–alkyl bond rather than a carbonyl–oxygen bond as is the case in other newly developed methods.[8] To examine whether the caesium salt method might be applicable to the synthesis of naturally occurring macrolides which usually have the hydroxy group on a secondary carbon atom, we carried out the reaction sequence shown in Scheme 2. The macrolide (**4**) was obtained from 2-methylcyclododecanone (**3**), which

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† Apparently this simple procedure succeeds because the caesium salts of aliphatic acids are soluble in DMF. This is not true of the caesium salts of aromatic acids and phenols that we previously examined (refs. 2—4); these salts were prepared in MeOH.

‡ Smaller-ring lactones can be opened with HBr—$MeCO_2H$ (ref. 7). Larger, less strained rings require the more reactive reagent HI–$MeCO_2H$.

was prepared by catalytic reduction of 2-methylenecyclododecanone, obtained by the method of Graz.[10] The high yield of (**4**) compared to its dimer (*cf.* **1**; $n = 11$, Table) indicates that displacement at a secondary carbon atom can take place without difficulty. The macrolide (**4**) has recently been reported to be a natural substance.[11]

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