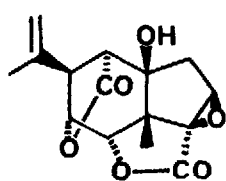


BISLACTONIZATION OF UNSATURATED DIACIDS USING LEAD TETRAACETATE

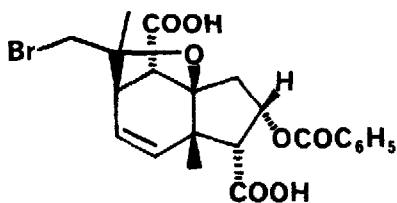
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Summary. The reaction of lead tetraacetate with unsaturated carboxylic acids (or salts) to form bis-lactones (γ or δ) can be controlled to produce efficiently cis addition of two carboxylic oxygens to the double bond, in consonance with an initial plumbolactonization step followed by S_N2 displacement of lead.

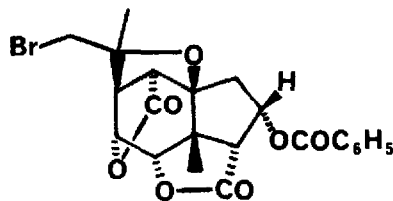
A key step in the recently reported¹ total synthesis of picrotoxinin (1) was the conversion of the diacid 2 to the bis- γ -lactone 3 in 99% yield by reaction with 6 equiv of lead tetraacetate in acetonitrile at 25° for 1.5 hr. This process finds precedent in the observation² that endo- Δ^4 -



1



2



3

bicyclo[2.2.1]heptene-1,2-dicarboxylic acid (4) upon heating at 100° with lead tetraacetate in acetic acid is converted into a bis- γ -lactone in ca. 60% yield. This letter is concerned with the scope, stereochemistry and mechanistic course of lead(IV) mediated bislactonization.

The bislactonization was studied under a wide variety of experimental conditions with the result that two satisfactory general procedures could be defined. The first procedure involves treatment of the free diacid usually in chloroform³ solution at 20-50° with 6 equiv of lead tetraacetate (Procedure A). A variant on these conditions which has been found to be more satisfactory with certain less reactive substrates is the use of acetonitrile as solvent at 80° with a larger excess of lead tetraacetate (Procedure A'). The second procedure utilizes the tetra-n-butylammonium salt of the diacid in acetonitrile at 75-80° with 6-15 equiv of lead tetraacetate (Procedure B). Since lead tetraacetate undergoes significant decomposition at 75-80° in acetonitrile, it is advisable either to add 6-8 equiv in several portions or to add 15 equiv at the start of the reaction. Five diverse substrates (4-8) were investigated as summarized in the Table. Although the reaction of a disalt according to Procedure B is slower than the bislactonization of the corresponding free diacid following Procedure A, the yields obtained by Procedure B are in general higher.

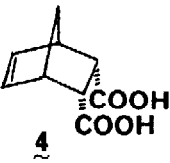
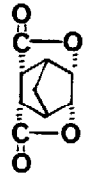
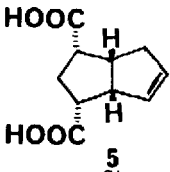
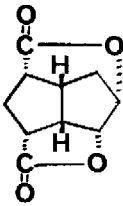
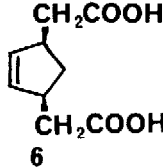
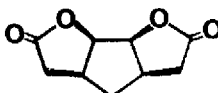
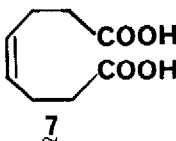
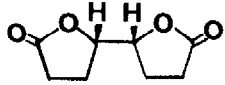
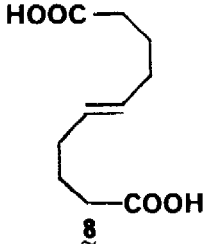
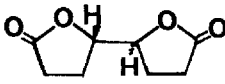
It is evident that the bislactonization of substrates 2, 4, 5, and 6 must follow a pathway of

cis addition of two oxygens to the carbon-carbon double bond because of geometrical constraints. For this reason the study of the stereoisomeric diacids 7 and 8 which can in principle undergo either cis or trans addition was included. The bislactonization of the cis diacid 7 was found to be completely stereospecific under all conditions studied, leading exclusively to the meso-bislactone by cis addition to C=C. In contrast, the trans diacid 8 was converted to a mixture of equal parts of d,l- and meso-bislactones by Procedure A. Modification of Procedure A by the addition of increasing amounts of pyridine led to greater amounts of the d,l-bislactone (ratio d,l to meso 3:1 with 100 equiv of pyridine). Bislactonization of the trans diacid 8 by Procedure B, however, furnished with > 95% specificity the d,l-product by cis addition. The results obtained with 7 and 8 are accommodated by the supposition that the first step involves Pb(IV) induced plumbolactonization (analogous to halo or mercuri-lactonization) and that this is followed by either S_N2 or S_N1 displacement of lead (in the Pb(III) mono lactone intermediate) by oxygen leading to bislactone. In the second step the S_N2 pathway becomes more favorable if carboxylate ion is the displacing nucleophile rather than the carboxylic acid function. Since the first step clearly would involve trans addition, S_N2 displacement in the second step would lead to overall cis addition as is observed in each case except for substrate 8 under the conditions of Procedure A. To the extent that the second step proceeds by the S_N1 mechanism stereorandomization can occur and both cis and trans C=C addition products will be observed. Thus the bislactonization of bis-salts (Procedure B) is expected to favor stereoselective cis addition relative to the use of free bis-acid. The greater propensity for stereoselective cis addition shown by the cis diacid 7 relative to the trans isomer 8 is possibly due to an S_N1 preference at the second stage with 8 as a consequence of assistance by the neighboring lactone oxygen to cation formation with a minimum of steric destabilization (i.e. repulsion between vicinal groups).

The investigation described herein demonstrates that the lead (IV) induced bislactonization of unsaturated diacids is a valuable synthetic method of considerable scope which compares very favorably with the silver salt-iodine bislactonization recently described.⁴ The experimental data which follow provide essential detail.⁵

Procedure A: Cis-4-octenedioic acid (25 mg, 0.14 mmol) was dissolved in 4 ml dry chloroform and lead tetraacetate⁶ (375 mg, 0.84 mmol, 6 equiv) was added in one portion. The solution was stirred for 72 hr at 23°, quenched with 20 μl ethylene glycol, diluted with 25 ml ethyl acetate, and filtered through Celite. The filtrate was evaporated and the residue was chromatographed on Florisil (10% acetone-chloroform) to afford the bis-lactone of meso-4,5-dihydroxyoctane-1,8-dioic acid (18.8 mg, 0.110 mmol, 78%) as colorless crystals, mp 104-105°, lit.⁴ 104-106°.

TABLE - BISLACTONIZATION OF SUBSTANCES 4 - 8

SUBSTRATE	PROCEDURE	PRODUCT	YIELD, mp
 <p>4</p>	A, 30 hr, 23° B, 6 hr, 75°		99+%, 263° 99+%, "
 <p>5</p>	A, 48 hr, 50° B, 48 hr, 75°		68%, 160° 85%, "
 <p>6</p>	A, 72 hr, 23° B, 30 hr, 75°		71%, 115° 89%, "
 <p>7</p>	A, 60 hr, 23° ^a B, 26 hr, 75° ^a		78%, 105° 98%, "
 <p>8</p>	A', 50 hr, 80° ^b B, 48 hr, 80° ^c		73%, - 86%, 55°

^a This reaction afforded meso-bislactone stereospecifically.

^b Product was a mixture (ca. 1:1) of meso- and d,l-bislactones.

^c Product was d,l-lactone with >20:1 stereoselectivity.

Procedure B: *trans*-4-Octenedioic acid (30 mg, 0.17 mmol) was treated with tetra-*n*-butylammonium hydroxide (0.34 mmol) in methanol. The solvent was removed and the residue was azeotroped with toluene and dried *in vacuo*. The crystalline tetra-*n*-butylammonium salt was dissolved in 4 ml dry acetonitrile and lead tetraacetate (1.15 g, 2.6 mmol, 15 equiv) was added. Reaction for 48 hr at 80° under argon and workup as above afforded a greater than 20:1 mixture respectively of the bislactones of *d,l*- and *meso*-4,5-dihydroxyoctane-1,8-dioic acid. Chromatography on Florisil (10% pentane-ethyl acetate) afforded the bislactone of *d,l*-4,5-dihydroxyoctane-1,8-dioic acid (25.1 mg, 0.147 mmol, 86.4%), mp 55°, lit. 55-56°.

Preparation of Unsaturated Diacids: Diacid **4** was prepared by the method of Diels and Alder.⁸ Cleavage of the more reactive double bond in dicyclopentadiene, followed by oxidation of the resulting dialdehyde, afforded diacid **5**.⁹ Diacid **6** was prepared by the method of Gassman and Creary.¹⁰ Diacid **7** was obtained from 1,5-cyclooctadiene via epoxidation, periodate cleavage, and oxidation.^{11a,b} Diacid **8** was prepared by two different methods. Overall olefinic inversion of dimethyl *cis*-4-octenedioate to *trans*-4-octenedioate was achieved via reaction of *d,l*-dimethyl 4,5-dihydroxyoctanedioate with dimethylformamide dimethyl acetal.^{12a,b} Diacid **8** was also directly available in good yield from the reaction of 2 equiv of dithio acetate¹³ with 1,4-dibromo-*trans*-2-butene (2 hr at -78 to 0°).^{14,15}

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