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Regioselective reactions on a 1,3-disubstituted dihydroxymethyl or dicarboxyl hexahydropentalene skeleton

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ABSTRACT

Iodo-, bromo-, chloro-etherification and oxymercuration–demercuration of hexahydropentalene 1,3-dimethanol were regioselectively realized with formation of pentalenofurane compounds in good yields. The corresponding hexahydropentaleno diacid and its monoester react regioselectively with MCPBA to give two γ-lactones. Haloetherification of the diacid also regioselectively gives halogenolactones in good yield. A new method for synthesis of a bislactone was developed in better yield (79%) than that presented in the literature (58%).

1. Introduction

In a previous paper[1] we presented MCPBA epoxidation of acyl-protected compounds **2**,[2] in which the expected *exo*-epoxides **3** are formed predominantly over the *endo*-epoxides **4**. When the unprotected compound **1** was used in the reaction with MCPBA, instead of the *exo*/*endo*-epoxides, we obtained the pentalenofurane compound **5** as the only product in over 90% yield.[1] This was attributed to the participation of the closer hydroxymethyl group in the epoxidation of the double bond (Scheme 1).

The molecular geometry of compound **1** put the hydroxymethyl group in close proximity to the double bond and thus made possible a regioselective reaction with MCPBA with formation of pentalenofurane compound **5** in high yield. We found in the literature that similar intramolecular addition reactions of hydroxyl (or carboxyl groups) to olefins were realized in high yields with catalysts such as silver(I) triflate,[3a] $Ln(OTf)_3$ in ionic liquids[3b] and $Co(nmp)_2$/*t*BOOH in air oxidation.[3c]

This MCPBA regioselective reaction on alkene-diol **1** stimulated us to study if other reactions on this particular skeleton also behave regioselectively (Scheme 2). We then extended our study to diacid **7**, with the same hexahydro-pentalene structure. We expected similar regioselective reactions to take place and obtain compounds with a γ-lactone structure **8** (Scheme 2) as a result of the closer carboxyl group participation in the reactions of the double bond. Herein we describe the results of this study.

2. Results and discussion

2.1. Chemistry

We first studied the *haloetherification* reactions of compound **1** with reagents like iodine/Na_2CO_3 or iodine/$NaHCO_3$, *N*-bromosuccinimide (NBS) or *N*-clorosuccinimide (NCS) (Scheme 3).

Iodoetherification of compound **1** was realized with iodine/Na_2CO_3 in acetonitrile[4] or with iodine/$NaHCO_3$ in dicloromethane[5] and resulted in selective formation of crystallized iodo-ether compound **6a** in 84.6% and respectively in 80.5% yield, by closing a tetrahydrofuran ring between the hydroxymethyl group and the closer carbon atom of the double bond. The iodine is linked *trans* to C–O of the tetrahydrofuran ring.

Treatment of compound **1** with NBS[5d,6] resulted also in selective formation of the corresponding crystallized bromoether **6b** in even

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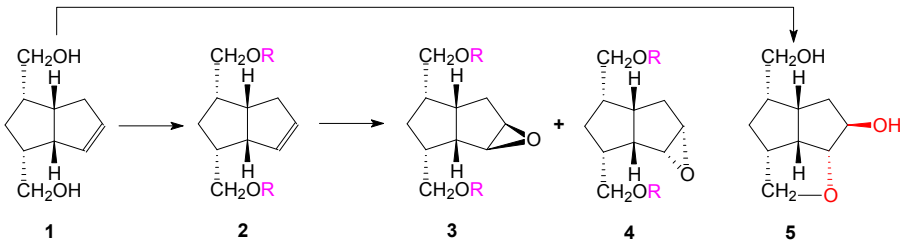
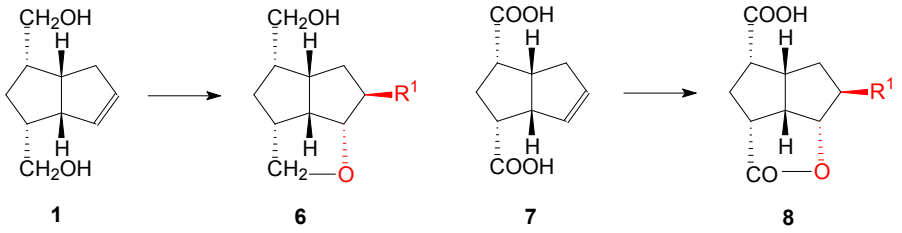
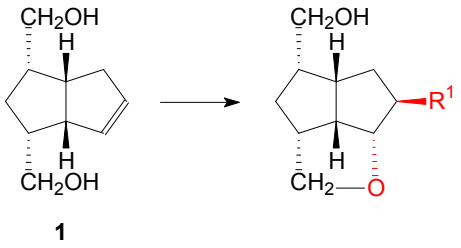


Scheme 1. MCPBA treatment of unprotected **1** or acyl-protected hexahydropentalene **2**.



Scheme 2. Pentalenofurane compounds **6** obtained from alkene **1** and lactone-acid compounds **8** obtained from diacid **7**.



6a, R^1 = I
6b, R^1 = Br
6c, R^1 = Cl
6d, R^1 = H

Scheme 3. Regioselective reactions of alkene-diol **1**.

better yield (96.5%). By similar treatment with NCS instead of NBS, the oily chloroether **6c** was obtained in lower isolated yield (58.5%). Like iodine, bromine and chlorine have the same *trans* correlation to C–O of the tetrahydrofuran ring. So, the configuration of the hydroxymethyl group closer to the double bond in compound **1** is responsible for the high regioselective halo-etherification to compounds **6a**–**6c** (Scheme 3).

Then we studied oxymercuration–demercuration of the double bond of compound **1** by already published procedures with mercuric acetate[7] and mercuric trifluoroacetate[8] and obtained the oily ether compound **6d** with the expected closing of the tetrahydrofuran ring, also in very good yields: 81% with $Hg(OAc)_2$ and 82.4%–91.6% yield with $Hg(BF_4)_2$ in 1:1 and 1.5:1 ratio of oxymercuration reagent/alkene respectively.

The pentalenofurane structure of compounds **6a**–**6d** was confirmed by NMR and of bromo-ether **6b** from this series by X-ray crystallography, as we had previously[1] done for compound **5** (Fig. 1).

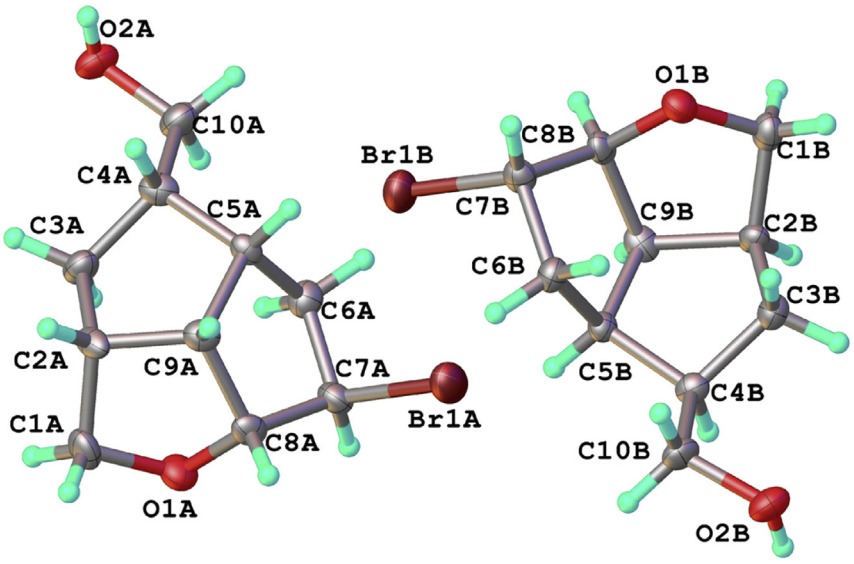
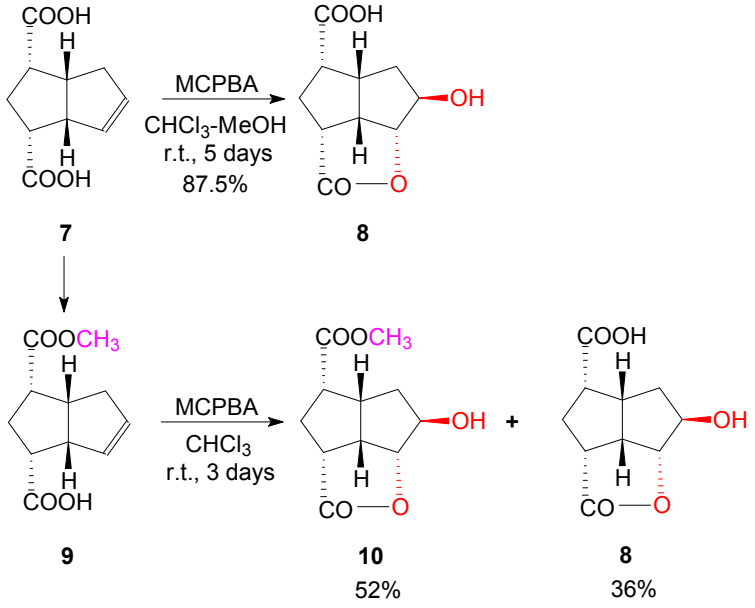


Fig. 1. Two crystallographic independent molecules in the crystal structure **6b**. Thermal ellipsoids are drawn at the 50% probability level.

Motivated by these good results on hexahydropentalene compound **1**, we studied the same reactions on compound **7**, with two diacid groups. First we studied the reaction of diacid **7** (obtained by oxidation of the corresponding dialdehyde with Jones reagent[9]) with MCPBA in the same conditions as those used for compound **1**,[1] and obtained the lactone-acid compound **8** as the sole product, in good yield (87.5%) (Scheme 4).

For obtaining hydroxyl-lactone, esters were used instead of γ-unsaturated carboxylic acids, with the same efficacy.[12,14] Hence, we extended the reaction to monomethyl ester **9** (obtained by esterification of potassium salt of the diacid **7** with methyl iodide in HMPT-THF (1:2) and obtained lactone **10**, in 52% yield, together with hydroxyl-acid lactone **8** in 26% yield; thus lactonization is realized in almost the same overall isolated yield (88%) as for diacid



Scheme 4. MCPBA treatment of alkene-diacid **7** and its monomethylester **9**.

We observed that diacid **7** reacted slower than alkendiol **1** and excess MCPBA reagent was used to complete the reaction.

A similar γ-lactonization with MCPBA, was realized in 61% yield on a pentalenofurane monocarboxylic acid,[10] or catalyzed by Amberlyst-15 ion exchange resin, in almost quantitative yield on the particular substrate: *cis*/*trans*-hex-4-enoic acid.[11] Instead of MCPBA, 30% H_2O_2 was used efficiently for lactonization of γ-unsaturated carboxylic acids (or esters) in the presence of catalysts like methyltrioxorhenium,[12] tungstic or molybdic acid.[13]

The structure of hydroxylactone-acid **8** was confirmed by NMR and unambiguously by X-ray crystallography, as shown in Fig. 2.

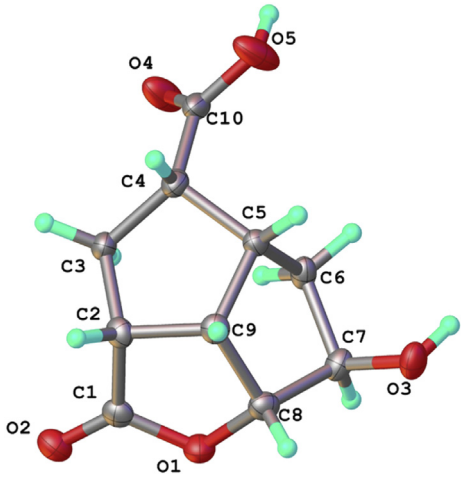


Fig. 2. X-ray molecular structure of lactone acid compound **8** with thermal ellipsoids at the 50% probability level.

7. This was expected due to the fact that diacid **7**, synthesized from *endo*-DCPD, (and monoester **9** as a consequence), is a mixture of two isomers with the double bond at C_4 or C_5 atoms. The structure of ester-lactone **10** has also been unambiguously confirmed by X-ray crystallography, as it can be seen from Fig. 3.

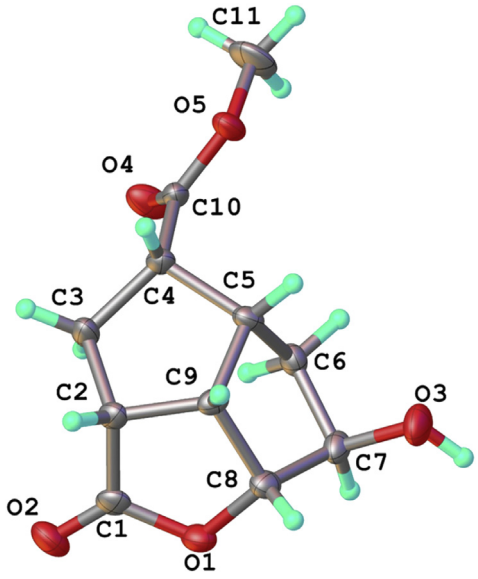
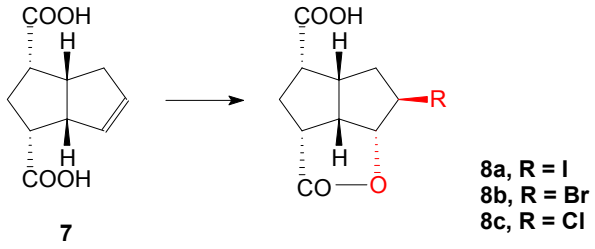


Fig. 3. X-ray molecular structure of lactone ester compound **10** with thermal ellipsoids at the 50% probability level.

In both cases, the functionalities generated in oxidation of alkene-diacid **7** and its monoester **9** with MCPBA are very clearly seen in Figs. 2 and 3, in which the 5-hydroxyl group is *exo* to the octahydropentalene skeleton and is in a *trans* correlation with C–O of the tetrahydrofuran ring.

We then realized halo-lactonization reactions of the diacid **7**, similar to those used in halo-etherification of the alkene-diol **1** (Scheme 5).



Scheme 5. Regioselective reactions of alkene-diacid **7**.

Iodo-lactonization of diacid **7** was realized in the following conditions: a) with two equivalents of iodine and sodium carbonate in acetonitrile[5d] in 54% yield **8a**; b) with iodine and sodium bicarbonate (2 and respectively 6 equiv) in DCM as solvent, in 89% yield; c) with sodium bicarbonate, potassium iodide and iodine (4, 6 and 1.1 equiv) in water as solvent,[15] in 78% and d) with 3.1 equiv of iodine (without base) in acetonitrile,[16] in 75.5% yield. The best yield was obtained in the method b).

In the first method a) we observed the formation of a by-product with R_f greater than that of the compound **8a**. Working in a mixture of water–chloroform as solvent (2.5:1), with excess base (K_2CO_3, 4 equiv) and also with two equivalents of iodine, we isolated the bis-lactone **11** in 79% yield, greater than that obtained with [hydroxyl(tosyloxy)iodo]benzene as reagent (58%).[17] This bis-lactone was the by-product formed in the first method. We suppose that bis-lactone **11** is formed by closing the second lactone ring (δ-lactone) from the iodo-lactone-acid **8a**, due to the excess of base used in the reaction, as in Scheme 6.

The synthesized compounds could be used as synthons in fine organic synthesis or synthesis of natural products, such as for example of verbenalol.

Detailed X-ray crystallography of **6b**, **8**, **10**, **8b** and **8c** compounds is presented in Supplementary data.

3. Conclusions

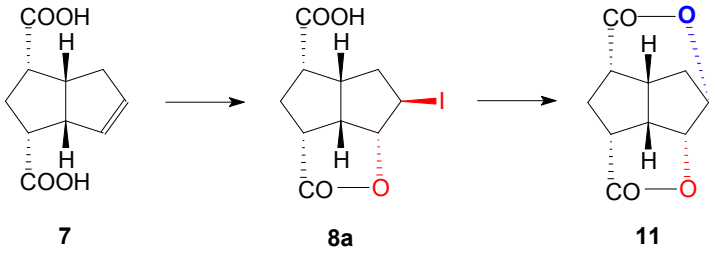
Halo-etherification (iodo-, bromo- and chloro-) and oxymercuration–demercuration of hexahydropentalene 1,3-dimethanol **1** was realized regioselectively to pentalenofurane compounds **6a**–**6d**, by intramolecular participation of the closer hydroxymethyl group in addition reactions of the double bond.

MCPBA reaction with diacid **7** and its monomethyl ester **9** takes place regioselectively to give γ-lactones **8** and **10**. Diacid **7** also reacts regioselectively with iodine, NBS and NCS, to give halogenolactones **8a**–**8c** in good yield. In the presence of excess K_2CO_3 as base, iodolactonization of diacid **7** gives bis-lactone **11** in 79% yield; this is a new method for synthesis of bis-lactone **11**, better than that presented in the literature (58%[17]).

4. Experimental

4.1. General

Melting points (uncorrected) were determined in open capillary on an OptiMelt melting point apparatus. Progress of the reaction was monitored by TLC on Merck silica gel 60 or $60F_{254}$ plates (Merck) eluted with the solvent system presented for each compound. Spots were developed with iodine and/or with sulfuric acid (15% in ethanol). IR spectra were recorded on a FTIR-100 Perkin Elmer spectrometer, in solid phase by ATR; frequencies are expressed in cm^{-1}, with the following abbreviations: w=weak, m=medium, s=strong, v=very, br=broad. MS were recorded on LTQ Orbitrap Velos Pro with ESI interface. Detection was realized for more abundant isotopic mass; fragments are given in parenthesis. ^1H NMR and ^{13}C NMR spectra are recorded on Varian Gemini 300 BB spectrometer (300 MHz for ^1H and 75 MHz for ^{13}C), chemical shifts are given in ppm relative to TMS as internal standard. Complementary spectra: 2D NMR and decoupling were done for correct assignment of NMR signals. The numbering of the atoms in compounds is presented in Schemes.



Scheme 6. Synthesis of bis-lactone **11** from **7**.

Bromo-lactonization in good yields of γ and δ-unsaturated carboxylic acids with NBS, but in the presence of different catalysts, is reported in the literature.[18] We realized bromo-lactonization and chloro-lactonization of diacid **7** with NBS, respectively with NCS, in the conditions specified for compound **1**, without any catalyst, in 75%, and respectively in 70.5% isolated yields. Some difficulties were encountered in these syntheses with isolation of the pure products from succinimide by-product. As in the MCPBA reaction, diacid **7** reacts slower with NBS and NCS than alkene-diol **1**.

The structure of both compounds was also unambiguously confirmed by X-ray crystallography, as it can be seen from Fig. 4a and b.

4.2. MCPBA treatment of diacid 7

6.17 g (31.45 mmol) (±)-(1α,3α,3aβ,6aβ)-1,2,3,3a,4,6a-hexahydropentalene-1,3-dicarboxylic acid **7** dissolved in 160 mL chloroform and 30 mL methanol were treated with 9.1 g (8.1 g 100%, 46.9 mmol) 89% MCPBA as previously described.[2] After 2 days, another 20 mmol MCPBA were added and stirred for 3 days at room temperature (rt). The solution was extracted with water (4×30 mL), the aqueous phases concentrated under vacuum and purified by

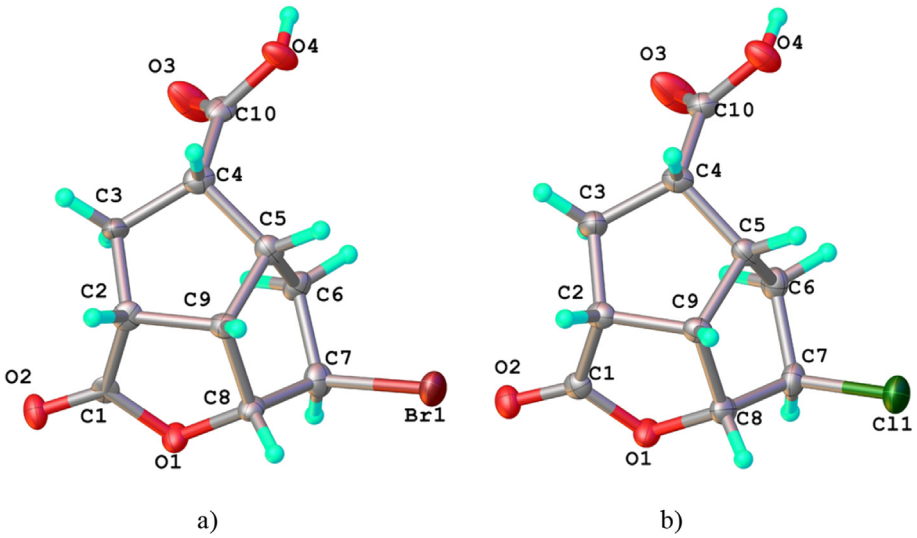


Fig. 4. X-ray molecular structure of bromo-lactone acid **8b** (a) and chloro-lactone acid **8c** (b) with thermal ellipsoids at the 50% probability level.

pressure chromatography, resulting in 5.84 g (87.5%) of pure compound **8** [(±)-(2aα,2a1β,4α,4aβ,6β,6aα)-6-hydroxy-2-oxooctahydro-2*H*-pentaleno[1,6-bc]furan-4-carboxylic] as an oil, which was crystallized from ethyl acetate–hexanes as white crystals: mp 180–184 °C, IR: 3503s, 2952w, 2912m, 1745vs, 1692vs, 1427m, 1356m, 1307m, 1287m, 1255m, 1194m, 1170s, 1035m, 1014s, 967w, 937m, 913m. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.57 (d,1H, J=7.0, H-6), 4.09 (d, 1H, J=3.7, H-5), 3.38 (dt, 1H, J=11.1, 7.0, H-6a), 3.12 (dd, 1H, J=11.0, 7.7, H-1), 3.09 (m, 1H, H-3), 3.02 (dq, 1H, J=11.2, 7.1, H-3a), 2.27 (ddd, 1H, J=13.8, 10.7, 8.2, H-2), 1.98 (ddd, 1H, J=13.8, 11.0, 7.7, H-2), 1.58 (dd, 1H, J=13.9, 7.1, H-4), 1.30 (ddd, 1H, J=13.9, 11.2, 3.7, H-4). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 180.1 (C-7), 173.8 (C-8), 87.4 (C-6), 75.4 (C-5), 48.8 (C-6a), 47.3 (C-1), 46.3 (C-3a), 42.1 (C-3), 31.9 (C-4), 30.8 (C-2). M wt 212, $[M-H]^-$: 211 [167 (1,3), 149 (1,2), 105 (1.1), 95 (1,6), 83 (100, BP)], MS: calcd for $C_{10}H_{12}O_5$+H: 213.0751; Found: 213.0751 [195].

4.3. MCPBA treatment of monomethylester of diacid compound

*4.3.1. Synthesis of monomethyl ester **9** of diacid **7**.* 1.97 g (10 mmol) Diacid **7**, 2.83 g (20.5 mmol) $KHCO_3$ in 20 mL HMPT and 40 mL THF were stirred for 1 h, 6 mL methyl iodide added and the mixture stirred at 60 °C overnight in a pressure vessel (TLC, ethyl acetate–hexane-acetic acid, 5:4:0.1, (I), R_f $_7$=0.44, R_f $_{monoester}$=0.53, R_f $_{diester}$=0.63). THF was distilled under reduced pressure, 100 mL benzene and 60 mL water added, phases separated, organic phase washed with 10 mL 20% sodium thiosulfate (aqueous phases extracted with 2×60 mL benzene), 10 mL brine, dried, concentrated and residue purified by pressure chromatography (ethyl acetate–hexane, 1:1), resulting in 850 mg (38%) of pure monoesters **9** (±)-(1α,3α,3aβ,6aβ)-3-(methoxycarbonyl)-1,2,3,3a,4,6a-hexahydropentalene-1-carboxylic acid as white crystals, IR: 3028m, 2961m, 2909m, 2800–2400 br, 1726vs (CO ester), 1686vs (CO-acid), 1433m, 1279m, 1251s, 1232s, 1196s, 1170s. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.79 (dq, 0.5H, J=5.6, 2.2, H-5), 5.77 (dq, 0.5H, J=5.6, 2.2, H-5), 5.55 (dq, 0.5H, J=5.8, 2.5, H-6), 5.37 (dq, 0.5H, J=5.8, 2.5, H-6), 3.70 (2s, 3H, CH_3), 3.59 (m, 1H, H-6a), 3.17 (m, 1H, H-3a), 2.99–2.84 (m, 2H, H-1, H-3), 2.55 (m, 1H, H-4), 2.12 (m, 1H, H-4), 2.05 (dd, 1H, J=12.6, 2.7, H-2), 1.96 (dt, 1H, J=12.6, 6.9, H-2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 179.5, 179.2 (2COOH), 173.8, 173.4 (2$COOCH_3$), 133.5, 133.2 (C-6), 128.9, 128.8 (C-6), 52.2, 52.0 (CH_3), 51.7, 51.7 (C-6a), 48.1, 48.1 (C-1 or C-3), 47.8, 47.7 (C-1 or C-3), 41.7, 41.6 (C-3a), 37.0 (C-4), 27.9 (C-2). MS: calcd for $C_{11}H_{14}O_4$+H: 211.0965; Found: 211.0913 [193, 179].

*4.3.2. MCPBA treatment of mono-methylester **9**.* 210.2 mg (1 mmol) Mono-methylester **9** in 10 mL $CHCl_3$ were treated with 0.37 g (1.5 mmol) 70% MCPBA and stirred for 3 days at rt (another 100 mg MCPBA were added). Solvent was removed under reduced pressure, and the crude product purified by pressure chromatography (ethyl acetate–hexanes, 1:1), resulting in 123 mg (52%) of pure compound **10**, methyl (±)-(2aα,2a1β,4α,4aβ,6β,6aα)-6-hydroxy-2-oxooctahydro-2*H*-pentaleno[1,6-bc]furan-4-carboxylate, as an oil with R_f=0.15, IR: 3446br m, 2955m, 1762s, 1728vs, 1437m, 1292m, 1158s, 1036s, 1014s. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.67 (dd, 1H, J=6.9, 1.4, H-6), 4.36 (d, 1H, J=3.6, H-5), 3.63 (s, CH_3), 3.44 (dt, 1H, J=11.3, 7.1, H-6a), 3.19 (dq, 1H, J=11.3, 6.9, H-3a), 3.11 (dd, 1H, J=11.0, 8.0, H-1), 3.07 (ddd, 1H, J=11.0, 8.0, 6.3, H-3), 2.44 (ddd, 1H, J=14.0, 10.7, 8.0, H-2), 2.27 (ddd, 1H, J=14.0, 11.3, 8.0, H-2), 1.71 (dd, 1H, J=14.6, 6.9, H-4), 1.53 (ddd, 1H, J=14.6, 11.3, 3.6, H-4). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 180.0 (C-7), 172.8 (C-8), 87.7 (C-6), 76.9 (C-5), 52.0 (CH_3), 49.2 (C-6a), 47.8 (C-1), 46.8 (C-3a), 42.5 (C-3), 32.5 (C-4), 31.2 (C-2), MS: calcd for $C_{11}H_{14}O_5$+H: 227.0914; Found: 227.0905 and 76.6 mg (36.1%) compound **8**.

4.4. Oxymercuration–demercuration of (±)-(1α,3α,3aβ,6aβ)-1,2,3,3a,4,6a-hexahydropentalene-1,3-diyl)dimethanol

4.4.1. With mercuric acetate. 5 mL THF were added to a solution of 3.19 g (10 mmol) mercuric acetate in 10 mL water. To the resulted yellow suspension, a solution of 1.68 g (10 mmol) (±)-(1α,3α,3aβ,6aβ)-1,2,3,3a,4,6a-hexahydropentalene-1,3-diyl)dimethanol in 10 mL tetrahydrofuran was added under stirring. After 3 min, the reaction mixture became a clear solution and was stirred for 2 h, monitoring the reaction by TLC [Silicagel, I, R_f $_{in}$=0.06, R_f $_{organomercuric}$=0.00, R_f $_{fin}$=0.22; acetone-extraction benzyne (70–80 °C), 2:1, R_f $_{in}$=0.64, R_f $_{fin}$=0.78]. The solution was cooled on an ice bath, 10 mL 3M NaOH and 10 mL 0.5M $NaBH_4$ in 3M NaOH were added, the cooling bath was removed and then the solution was stirred until it became clear. Solid ammonium sulfate was added, phases separated, and aqueous phase extracted with tetrahydrofuran (4×30 mL). Combined organic phases were washed with satd $(NH_4)_2SO_4$ soln (15 mL), dried (Na_2SO_4), concentrated, co-evaporated with benzene, and the crude product (1.722 g) was purified by pressure chromatography (eluent: extraction benzyne-

acetone, 1:1), resulting in 1.36 g (81%) of pure compound **6d** (±)-((2aα,2a1β,4α,4aβ,6aα)-octahydro-2*H*-pentaleno[1,6-bc]furan-4-yl)methanol as oil, IR (2% in $CHCl_3$): 3580, 2900, 2860, 2840, 1450, 1060. ^{1}H-RMN (DMSO-d_6, 300 MHz): δ 4.40 (t, J=5.1, O*H*, deuterable), [4.38 (d, 1H, J=4.1, H-5) +TFA], 4.07 (dd, 1H, J=6.3, 3.3, H-6), 3.53 (d, 1H, J=8.7, H-7), 3.35 (dd, 1H, J=8.7, 5.0, H-7), 3.33 (dd, 2H, J=7.1, H-8), 2.87 (dt, 1H, J=9.2, 6.3, H-6a), 2.54 (dq, 1H, J=9.2, 5.0, H-1), 2.37 (dq, 1H, J=9.8, 7.4, H-3a), 2.04 (hept, 1H, J=6.8, H-3), 1.84 (dd, 1H, J=12.6, 4.4, H-2), 1.82 (ddd, 1H, J=12.8, 8.5, 5.7, H-4), 1.46–1.22 (m, 3H, H-4, 2H-5), 0.95 (td, 1H, J=12.6, 9.8, H-2). ^{13}C-RMN (DMSO-d_6, 75 MHz): δ 84.3 (C-6), 72.8 (C-7), 62.1 (C-8), 54.4 (C-6a), 47.2 (C-3), 45.6 (C-3a), 44.1 (C-1), 33.8 (C-2), 33.4 (C-5), 23.7 (C-4). MS: m/e: [M−1]: 167, [150, 132, 119, 117, 106, 93, 91, 79 (100%)], MS: calcd for $C_{10}H_{16}O_2$+H: 169.1223; Found: 169.1218 [151, 137, 123].

4.4.2. With mercuric tetrafluoroborate. By replacing mercuric acetate with mercuric tetrafluoroborate, at the same ratio of 1:1 alkene/mercuric tetrafluoroborate, the yield of **6d** was 82.4%. With a ratio of 1.5:1 alkene/mercuric tetrafluoroborate, the yield of **6d** was 91.6%. [The mercuric tetrafluoroborate solution was prepared from 3.25 g (15 mmol) HgO and 5.32 mL (33 mmol) 44.3% (g/g) HBF_4, 5 mL water and 10 mL THF added and cooled on an ice bath prior to addition of alkene; the final product was extracted with ethyl ether].

4.5. Iodoetherification of (±)-(1α,3α,3aβ,6aβ)-1,2,3,3a,4,6a-hexahydropentalene-1,3-diyl)dimethanol

4.5.1. With iodine and sodium carbonate.[4] To a mixture of 1.523 g (6 mmol) iodine and 636 mg (6 mmol) anh. Na_2CO_3, a solution of 505 mg (3 mmol) compound **1** in 50 mL acetonitrile (instead of CH_2Cl_2) was added under stirring and the mixture was further stirred at rt monitoring the reaction by TLC (Silica gel, I, 5:4:0.1, $R_{f\ \mathbf{1}}$=0.58, $R_{f\ \mathbf{6a}}$=0.36). In two hours, alkene compound was quantitatively transformed in the iodo-ether compound **6a**. 25 mL 20% Sodium thiosulfate were added, phases separated, organic phase washed with 15 mL 20% sodium thiosulfate, 20 mL brine, dried (anh. $MgSO_4$) and concentrated. [Aqueous phases were extracted with ethyl acetate (20 mL) and combined with the concentrate]. The crude product (0.97 g) was purified by pressure chromatography (eluent: hexane–ethyl acetate, 2.5:1), resulting in 0.745 g (84.6%) of pure compound **6a** (±)-((2aα,2a1β,4α,4aβ,6β,6aα)-6-iodooctahydro-2*H*-pentaleno[1,6-bc]furan-4-yl)methanol as white crystals, mp 69.2–71.4 °C, IR: 3385br s, 2954s, 2937s, 2852vs, 1420m, 1176m, 1062s, 1016s, 994s, 937m, 909s, 593m. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.42 (t,1H, J=5.2, *H*–O deuterable), 4.42 (d, 1H, J=5.1, H-5), 4.41 (d, 1H, J=5.9, H-6), 3.63 (d,1H, J=8.5, H-7), 3.43 (dd,1H, J=8.5, 5.1, H-7), 3.35 (dd,1H, J=10.6, 6.3, H-8), 3.26 (dd, 1H, J=10.6, 8.1, H-8), 3.15 (dt, 1H, J=8.8, 5.9, H-6a), 2.83 (m, 1H, H-3), 2.61 (dq,1H, J=9.3, 5.1, H-1), 2.13 (m, 1H, H-3a), 1.93 (m, 1H, H-2), 1.89 (dd, 1H, J=14.5, 5.1, H-4), 1.82 (dd, 1H, J=14.5, 7.5, H-4), 0.96 (dt, 1H, J=12.6, 9.7, H-2). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 91.7 (C-6), 73.7 (C-7), 61.8 (C-8), 53.1 (C-6a), 46.1 (C-3), 45.0 (C-3a), 43.3 (C-1), 35.1 (C-5), 34.8 (C-2), 34.3 (C4), MS: calcd for $C_{10}H_{15}IO_2$+H: 295.0190; Found 295.0184 [277, 167, 259, 149].

4.5.2. With iodine and sodium bicarbonate.[5] To a mixture of 2.284 (9 mmol) iodine and 756 mg (9 mmol) $NaHCO_3$, a solution of 505 mg (3 mmol) compound **1** in 60 mL dichloromethane was added under stirring, monitoring the reaction by TLC. After similar work-up, 825 mg crude product were obtained, which after column chromatography purification gave 710 mg (80.5%) of pure compound **6a**.

4.6. Iodolactonization of (±)-(1α,3α,3aβ,6aβ)-1,2,3,3a,4,6a-hexahydropentalene-1,3-dicarboxylic acid 7

4.6.1. With Na_2CO_3 and iodine in acetonitrile. 5 mmol (981 mg) Diacid **7** were treated as in 5.4 with iodine (10 mmol, 2.54 g) and Na_2CO_3 (10 mmol, 1.06 g) in 60 mL acetonitrile, monitoring the reaction by TLC (I, $R_{f\ \mathbf{7}}$=0.34, $R_{f\ \mathbf{8a}}$=0.07). After acidulation to pH 2 with conc. HCl and reduction of excess iodine with 20% sodium thiosulfate soln, the product was extracted with ethyl acetate and purified by pressure chromatography (ethyl acetate–hexane, 1:1), resulting in 870 mg (54%) of pure product **8a**, (±)-(2aα,2a1-β,4α,4aβ,6β,6aα)-6-iodo-2-oxooctahydro-2*H*-pentaleno[1,6-bc]furan-4-carboxylic acid as white crystals, mp 204–205.5 °C (ethyl acetate), IR: 3101ms, 2961ms, 1728vs, 1438w, 1359ms, 1280m, 1216s, 1203s, 1180s, 1150s, 998s, 857ms, 651w. ^{1}H NMR-300 MHz 65 °C (DMSO-d_6, ppm, J Hz): δ 12.15 (OH), 5.17 (d, 1H, J=6.8, H-6), 4.58 (d, 1H, J=4.9, H-5), 3.53 (dt, 1H, J=11.0, 6.8, H-6a), 3.25–3.15 (m, 3H, H1, H-3, H-3a), 2.43 (ddd, 1H, J=13.7, 10.6, 5.8, H-2), 2.08 (ddd, 1H, J=13.7, 10.4, 7.5, H-2), 1.95 (dd, 1H, J=15.0, 6.4, H-4), 1.78 (ddd, 1H, J=15.0, 10.6, 4.9, H-4). ^{1}H NMR (DMSO-d_6 + C_6D_6, 300 MHz): δ 5.18 (d, 1H, J=6.8, H-6), 4.58 (d, 1H, J=4.9, H-5), 3.51 (dt, 1H, J=11.0, 7.5, H-6a), 3.30 (dq, 1H, J=11.0, 7.1, H-3a), 3.23 (dd, 1H, J=11.0, 7.8, H-1), 3.20 (dd, 1H, J=11.0, 7.5, H-3), 2.48 (dd, 1H, J=13.9, 10.6, H-2), 2.17 (ddd, 1H, J=13.9, 11.0, 7.6, H-2), 2.00 (dd, 1H, J=15.0, 6.8, H-4), 1.83 (ddd, 1H, J=15.0, 11.0, 4.9, H-4). ^{13}C NMR (DMSO-d_6, ppm, 75 MHz): δ 179.5 (C-7); 173.5 (C-8); 89.8 (C-6); 48.7 (C-6a); 47.4 (C-1); 46.7 (C-3a); 42.3 (C-3); 35.0 (C-4); 31.6 (C-2). 31.5 (C-5), MS: calcd for $C_{10}H_{11}IO_4$+H: 322.9775; Found: 322.9767 [304, 250, 195].

4.6.2. With $NaHCO_3$ and iodine in dichloromethane. 2 mmol (392.4 mg) Diacid **7** were treated with 4 mmol (336.5 mg) $NaHCO_3$ in 10 mL methanol, stirred for 1 h at 50 °C, solvent was removed under vacuum and residue co-evaporated with benzene (2×10 mL). Dichloromethane (50 mL) and $NaHCO_3$ (168 mg, 2 mmol) were added, the mixture was cooled on an ice-water bath, iodine (2 mmol, 507.6 mg) was added in portions and the mixture was stirred overnight. The mixture was treated with 20% sodium thiosulfate soln, acidified with conc. HCl to pH 2, cooled on an ice-bath, the product filtered, washed with water (2×10 mL), dried and recrystallized from ethyl acetate, resulting in 0.43 g of pure compound **8a**. Dichloromethane solution was washed with water (10 mL) (All aqueous phases extracted with 2×20 mL dichloromethane), concentrated, unified with mother liquors from crystallization and purified by pressure chromatography as above, resulting in 166.6 mg of compound **8a** (total yield 89.4%).

4.6.3. With $NaHCO_3$, iodine, KI in water. 3 mmol (588.6 mg) Diacid **7** were added to a soln of 12 mmol (1.09 g) $NaHCO_3$ in 30 mL water and stirred for 10 min. Then a solution of 18 mmol (2.99 g) KI and 3.2 mmol (812 mg) iodine in 30 mL water[15] was added and stirred overnight. After work-up as above, 754 mg (78%) of compound **8a** were obtained.

4.6.4. With iodine in acetonitrile. 3 mmol (588.6 mg) Diacid **7** were dissolved in 30 mL acetonitrile, the solution was cooled on an ice-water bath, 9.5 mmol (2.41 g) iodine[16] were added and stirred overnight. After work-up as in 5.5 b) (extraction with ethyl acetate) 0.73 g (75.5%) of pure compound **8a** were obtained.

4.7. Synthesis of bis-lactone 11

Diacid **7** (2 mmol, 588.6 mg) was added to a solution of K_2CO_3 (1.104 g, 8 mmol) in water (50 mL), the solution was stirred for 10 min, chloroform (20 mL) was added, the reaction mixture was cooled on an ice-water bath, iodine (1.015 g, 4 mmol) was added in

portions in 15 min and stirred overnight, monitoring the reaction by TLC (I, twice eluted, R_f **11**=0.18). 20% Sodium thiosulfate (12 mL) was added, the solution acidified to pH 2 with conc. HCl, extracted with dichloromethane (4×30 mL), organic phase was washed with water (15 mL), dried, concentrated and the product crystallized from ethyl acetate, resulting in 206 mg (79%) of pure bis-lactone **11** as white crystals, mp 244.5–246.0 °C. (lit.[9] 244–245.5C), IR: 2959, 2944, 1764, 1725, 1447, 1380, 1320, 1246, 1183, 1158, 1106, 1055, 1032, 1005, 991. ^{1}H NMR- (DMSO-d_6, 300 MHz 65 °C): δ 4.98 (dd, 1H, J=9.9, 4.7, H-6), 4.86 (dq, 1H, J=3.0, 1.4, H-5), 3.30 (dt, 1H, J=9.6, 1.4, H-6a), 3.15 (tt, 1H, J=6.6, 1.4, H-3), 3.08 (dt, 1H, J=9.3, 1.9, H-1), 2.86 (m, H-3a), 2.47 (dt, 1H, J=14.0, 1.9, H-2), 2.39 (ddd, 1H, J=14.0, 9.3, 7.4, H-2), 2.18 (d, 1H, J=14.0, H-4), 1.87 (ddd, 1H, J=14.0, 4.1, 2.4, H-4). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 179.0 (C-7), 171.6 (C-8), 83.5 (C-6), 78.2 (C-5), 48.3 (C-3), 47.7 (C-6a), 44.3 (C-3a), 43.5 (C-1), 38.3 (C-2), 31.2 (C-4), MS: calcd for $C_{10}H_{10}O_4$+H: 195.0652, found: 195.0650 [177, 167, 149, 121].

Mother liquors were concentrated and purified by pressure chromatography (eluent: ethyl acetate–hexane, 1:1), resulting in 101 mg of pure compound **11** (total yield: 79%) (Lit.[17] 58%).

4.8. Bromoetherification of (±)-(1α,3α,3aβ,6aβ)-1,2,3,3a,4,6a-hexahydropentalene-1,3-diyl)dimethanol

2.67 g (15 mmol) NBS were added to a solution of 1.68 g (10 mmol) diole **1** in 50 mL acetone and 5 mL water and the mixture was stirred at rt for 2 h, monitoring the reaction by TLC (I, R_f **1**=0.26, R_f **6b**=0.51). The solvents were removed under vacuum, co-evaporated with toluene. Most of succinimide was crystallized from toluene (15 mL) and filtered. The filtrate was concentrated and purified by pressure chromatography (ethyl acetate–hexane, 1:1), resulting in 2.39 g (96.5%) of pure product **6b** [(±)-((2aα,2a1-β,4α,4aβ,6β,6aα)-6-bromooctahydro-2*H*-pentaleno[1,6-bc]furan-4-yl)methanol]. A fraction crystallized from ethyl acetate–hexane as white crystals has mp 62.5–63.5 °C, IR: 3317, 2942, 2854, 1068, 1018, 943, 911, 647. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.47 (d, 1H, J=4.3, H-5), 4.26 (d, 1H, J=5.8, H-6), 3.61 (d, 1H, J=8.7, H-7), 3.42 (m, 1H, H-7), 3.35 (dd, 1H, J=10.6, 6.5, H-8), 3.27 (dd, 1H, J=10.6, 8.0, H-8), 3.15 (dt, 1H, J=9.1, 5.8, H-6a), 2.81 (m, 1H, H-3a), 2.63 (dq, 1H, J=8.7, 5.0, H-1), 2.13 (hept, 1H, J=6.5, H-3), 1.98 (ddd, 1H, J=14.7, 10.4, 4.3, H-4), 1.87 (ddd, 1H, J=12.7, 8.7, 5.0, H-2), 1.84 (dd, 1H, J=14.7, 7.1, H-4), 0.96 (dt, 1H, J=12.7, 9.8, H-2). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 90.1 (C-6), 73.8 (C-7), 61.9 (C-8), 57.4 (C-5), 53.1 (C-6a), 46.3 (C-3), 44.2 (C-3a), 43.4 (C-1), 34.0 (C-2), 33.6 (C4), MS: calcd for $C_{10}H_{15}BrO_2$+H: 247.0328; Found: 247.0325 [229, 167, 149, 121].

4.9. Bromolactonization of (±)-(1α,3α,3aβ,6aβ)-1,2,3,3a,4,6a-hexahydropentalene-1,3-dicarboxylic acid 7

1.96 g (10 mmol) Diacid **7** were dissolved in 50 mL acetone and 5 mL water, 2.67 g (15 mmol) NBS were added and stirred at rt, monitoring the reaction by TLC (I, R_f **7**=0.42, R_f **8b**=0.48). The reaction mixture was filtered, washed with acetone (ATTENTION, work in a ventilated hood, because some bromoacetone is formed, which is lacrimatory), filtrated, concentrated under reduced pressure and purified by pressure chromatography, resulting in 2.08 g (75.4%) of crystallized compound **8b** (isopropanol) (±)-(2aα,2a1-β,4α,4aβ,6β,6aα)-6-bromo-2-oxooctahydro-2*H*-pentaleno[1,6-bc] furan-4-carboxylic acid as white crystals, mp 216–218 °C, IR: 3456br m, 2969w, 2878w, 1704vs, 1454w, 1317m, 1271s, 1118m, 1050m, 735m. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.04 (d, 1H, J=7.0, H-6), 4.63 (d, 1H, J=3.6, H-5), 3.53 (dt, 1H, J=11.0, 7.0, H-6a), 3.22 (dd, 1H, J=11.0, 7.7, H-1), 3.20–3.10 (m, 2H, H-3, H-3a), 2.37 (ddd, 1H, J=13.8, 10.6, 8.8, H-2), 2.02 (ddd, 1H, J=13.8, 10.6, 7.7, H-2), 1.95 (dd, 1H, J=15.3, 6.5, H-4), 1.87 (ddd, 1H, J=15.3, 10.6, 3.6, H-4). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 179.3 (C-7), 173.4 (C-8), 87.7 (C-6), 55.0 (C-5), 48.6 (C-6a), 46.8 (C-1), 46.4 (C-3a), 40.2 (C-3), 33.7 (C-4), 31.2 (C-2). M wt 274/276; [M−H]$^-$: 273/275 [79/81(100, BP) [Br−], MS: calcd for $C_{10}H_{11}BrO_4$+H: 274.9914; Found: 274.9913 [256].

4.10. Chloroetherification of (±)-(1α,3α,3aβ,6aβ)-1,2,3,3a,4,6a-hexahydropentalene-1,3-diyl)dimethanol

2.19 g (13 mmol) Diol **1** in 65 mL acetone and 6.5 mL water were treated with 2.7 g (19.5 mmol) 97% NCS and refluxed overnight, monitoring the reaction by TLC (hexane–ethyl acetate-acetic acid, 5:2:0.1, R_f **1**=0.08, R_f **6c**=0.22). The reaction mixture was decolorized with active charcoal, filtered, washed with hot acetone, the filtrate was concentrated and the concentrate was dissolved in hot toluene. Succinimide crystallized on cooling and was filtered, the filtrate concentrated and purified by pressure chromatography (eluent: hexane–ethyl acetate, 2:1), resulting in 1.54 g (58.5%) of pure **6c** [(±)-((2aα,2a1β,4α,4aβ,6β,6aα)-6-chlorooctahydro-2*H*-pentaleno [1,6-bc]furan-4-yl)methanol], as an oil, IR: 3428br m, 2961vs, 2936s, 2861s, 1074s, 1022s, 997vs, 947m, 812w, 719w, 672w. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.42 (d, 1H, J=4.1, H-5), 4.41 (t, 1H, J=5.1, OH, deuterable), 4.12 (d, 1H, J=6.3, H-6), 3.71 (d, 1H, J=8.7, H-7), 3.46 (dd, 1H, J=8.7, 5.2, H-7), 3.35 (ddd, 1H, J=10.7, 6.5, 5.1, H-8, with TFA became dd, J=10.7, 6.5), 3.28 (ddd, 1H, J=10.7, 8.0, 5.1, H-8, with TFA became dd, J=10.7, 8.0), 3.14 (dt, 1H, J=9.1, 6.3, H-6a), 2.78 (m, 1H, H-3a), 2.64 (dq, 1H, J=9.5, 5.2, H-1), 2.13 (hept, 1H, J=6.5, H-3), 1.86 (dd, 1H, J=14.3, 4.1, H-4), 1.83 (m, 1H, H-2), 1.76 (dd, 1H, J=14.3, 7.5, H-4), 0.97 (dt, 1H, J=12.7, 9.8, H-2). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 89.6 (C-6), 73.7 (C-7), 65.0 (C-5), 61.8 (C-8), 53.0 (C-6a), 46.5 (C-3), 43.7 (C-3a), 43.4 (C-1), 33.8 (C-2), 32.9 (C4), MS: calcd for $C_{10}H_{15}ClO_2$+H: 203.0833; Found: 203.0830 [185, 167, 149, 121].

4.11. Chlorolactonization of (1*R*,3*S*,3a*R*,6a*S*)-1,2,3,3a,4,6a-hexahydropentalene-1,3-dicarboxylic acid 7

2.55 g (13 mmol) Diacid **7** were treated with NCS as in the above example. 2 g More NCS were used and the reflux was continued for 24 h. TLC (I, R_f **7**=0.34, R_f **8c**=0.21). After similar work-up, 2.115 g (70.5%) of pure crystallized compound **8c**, (±)-(2aα,2a1-β,4α,4aβ,6β,6aα)-6-chloro-2-oxooctahydro-2*H*-pentaleno[1,6-bc] furan-4-carboxylic acid as white crystals were obtained as white crystals, mp 228.1–229.3 °C, IR: 3095s, 2970s, 1732vs, 1357m, 1223s, 1205s, 1182s, 1154s, 1064s, 867m. ^{1}H NMR-300 MHz (DMSO-d_6, ppm, J Hz): δ 12.44 (OH), 4.90 (dd,1H, J=7.0, 1.1, H-6), 4.60 (d, 1H, J=3.8, H-5), 3.53 (dt, 1H, J=11.2, 7.1, H-6a), 3.22 (dd, 1H, J=11.0, 7.6, H-1), 3.17 (m, 1H, H-3), 3.12 (dq, 1H, J=10.8, 7.1, H-3a), 2.35 (ddd, 1H, J=14.0, 11.0, 8.2, H-2), 2.02 (ddd, 1H, J=14.0, 11.0, 7.6, H-2), 1.89 (dd, 1H, J=15.0, 7.1, H-4), 1.77 (ddd, 1H, J=15.0, 10.8, 3.8, H-4). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 179.4 (C-7), 173.5 (C-8), 87.4 (C-6), 63.7 (C-5), 48.7 (C-6a), 47.0 (C-1), 46.0 (C-3a), 42.1 (C-3), 33.4 (C-4), 31.0 (C-2), M wt 230/232 (3/1), [M−H]$^-$: 229/231 (3/1) [193 (100, BP), 149], MS: calcd for $C_{10}H_{11}ClO_4$+H: 231.0419; Found: 231.0412 [213].

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Supplementary data

Supplementary data (^{1}H NMR and ^{13}C NMR spectra for compounds, crystallography data in Tables 1S and 2 for compounds **6b**, **8**, **10**, **8b** and **8c**, Figures 1S to 4S, X-ray discussion and experimental data) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.07.021. These data include

MOL files and InChiKeys of the most important compounds described in this article.

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