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SYNTHESIS OF NEW DIHYDROXY-DIOXYGENATED *ortho*-[2,x]CYCLOPHANES

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Abstract - The synthesis of title compounds (**1a-f**) by intramolecular reductive coupling is presented. The reaction is carried out in water solution, in the presence of Zn or Al powder, in basic media.

INTRODUCTION

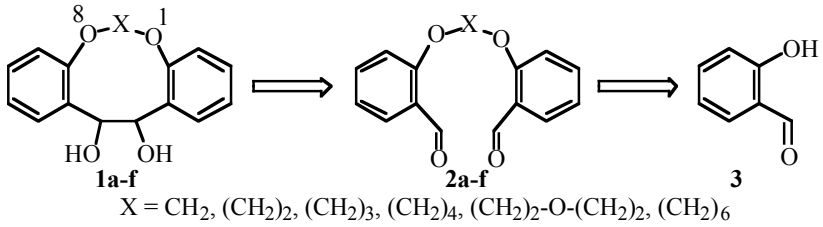
The reductive coupling of carbonyl compounds using different catalytic systems (such as metals, low-valent early transition metal species, salts or complexes) is known as pinacol coupling reaction, and various reducing agents for this reaction have been developed extensively over the last three decades.[1] This particular method for constructing carbon-carbon bond, subsequently 1,2-diols, by reductive coupling of carbonyl compounds has received far more attention as an intermolecular process than as an intramolecular one. Nevertheless, several intramolecular versions of the above reaction were effectively employed as key steps in the total synthesis of some complex natural and unnatural products. Thus, we can easily classify the intramolecular reductive coupling processes as: 1) starting from aliphatic dialdehydes;[2] 2) starting from thioether dicarbonyl compounds;[3] 3) starting from biphenyl derivatives;[4] 4) used in syntheses of natural products (such as taxoid ring systems,[5] trehazoline[6] or trehazolamine,[7] inositol derivatives,[8] cembranoids[9] or other terpenoids[10]). Furthermore, these syntheses imply the use of sophisticated reagents in carefully chosen reaction conditions. We developed recently a new method for performing the reductive coupling of carbonyl or imine compounds that proved to be effective in aqueous conditions, in the presence of cheap, commercially available metallic powders of Al or Zn, in a basic media (usually 10% aqueous NaOH solution).[11] This method has already been applied to the single-step synthesis of tetrahydroxy[2,2]*meta*-cyclophanes *via* pinacol coupling reaction of 1,3-benzene dicarboxaldehydes.[12]

We wish to report now the synthesis of a series of bridge-hydroxylated [2,x]*ortho*-cyclophanes (x=3~8),

with two hydroxyl groups in the first bridge and two or three oxygen atoms in the second bridge, namely 4,5-dihydroxy-1,8-dioxy-2,3:6,7-dibenzocyclononane (**1a**), 4,5-dihydroxy-1,8-dioxy-2,3:6,7-dibenzocyclodecane (**1b**), 4,5-dihydroxy-1,8-dioxy-2,3:6,7-dibenzocycloundecane (**1c**), 4,5-dihydroxy-1,8-dioxy-2,3:6,7-dibenzocyclododecane (**1d**), 4,5-dihydroxy-1,8,11-trioxy-2,3:6,7-dibenzo-cyclotridecane (**1e**) and 4,5-dihydroxy-1,8-dioxy-2,3:6,7-dibenzocyclotetradecane (**1f**), respectively.

RESULTS AND DISCUSSIONS

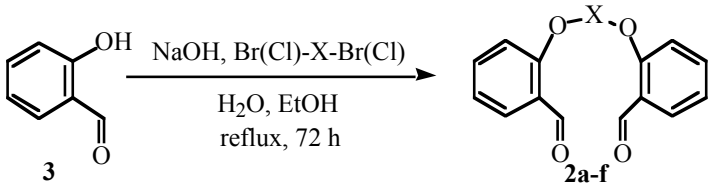
Our approach strategy to the target molecules involves the intramolecular reductive coupling of aromatic aldehydes connected by a dietheric bridge. Such compounds can be readily obtained, using a two-step synthesis, from salicylaldehyde, as presented in the retrosynthetic scheme:



Scheme 1 *Retrosynthesis scheme for diols (**1a-f**)*

We have already investigated the behavior of *o*- and *p*-anisaldehydes toward pinacol coupling.[11c] Both proved to be favorable substrates, yielding consequently the corresponding diols. We decided therefore to submit some compounds with structures of type (**2a-f**) to the intramolecular reductive coupling. Moreover, a scrutinized investigation of the chemical literature showed us no mentions of diols with structures of title molecules (**1a-f**).

Previous reports on the synthesis of some dialdehydes of type (**2**) showed two groups of processes: a) the transformation of salicylaldehyde into the corresponding sodium alcoxyde and a subsequent Williamson reaction with a dibrominated compound, in reflux of DMF[13] or b) a one-pot reaction among salicylaldehyde, a dihalogenated compound and NaOH, without isolation of the sodium salt, in boiling alcohol/NaOH solution[14] or boiling THF/HMPA solution.[15] We performed the syntheses of compounds (**2a-f**) as one-pot reactions, using salicylaldehyde and the corresponding dibrominated compounds, in ethanol and in the presence of a diluted aqueous NaOH solution. All reactions were carried out by refluxing the reaction mixture for 72 h. We also found out that nitrogen flow is not necessary (there are no changes concerning the total yield of the reaction), as it was previously mentioned in literature data.[14]



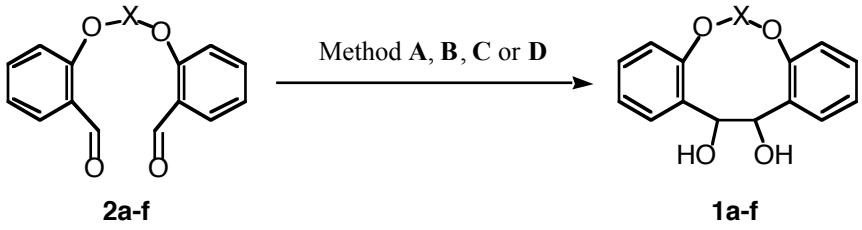
Scheme 2 *Synthesis of dialdehydes (**2a-f**)*

Table 1. Synthesis of dialdehydes (**2a-f**)

Cpd.	X	Yield (%)	mp (˚C) (lit.,[13a] mp)
2a	$-CH_2-$	57	131 (131-132)
2b	$-(CH_2)_2-$	45	130 (130-131)
2c	$-(CH_2)_3-$	62	98 (97-98)
2d	$-(CH_2)_4-$	64	112 (112.5-113.5)
2e	$-(CH_2)_2-O-(CH_2)_2-$	56	73.5-75 (66-67[14a])
2f	$-(CH_2)_6-$	23[a)]	77-79 (79.5-80)

a) 1,6-Dichlorohexane was used instead of the corresponding dibrominated compound.

Pinacol intramolecular condensations of compounds (**2a-f**) were carried out in 10% aqueous NaOH solution and in the presence of Zn or Al powder. The dialdehyde was dispersed in 10 mL of ethanol, the metallic powder (Zn or Al) was added and after that the NaOH solution was poured into the reaction flask, in one portion. The reaction mixture was kept at 60˚C and ultrasonication for 5 h, under mechanical stirring (for Methods **A** and **B**), or at room temperature and magnetical stirring, for 5 h (for Methods **C** and **D**). The results of these processes are summarized in **Table 2**.



2a-f **1a-f**

Scheme 3 *Synthesis of diols (**1a-f**)*

Table 2. Syntheses of diols (**1a-f**)

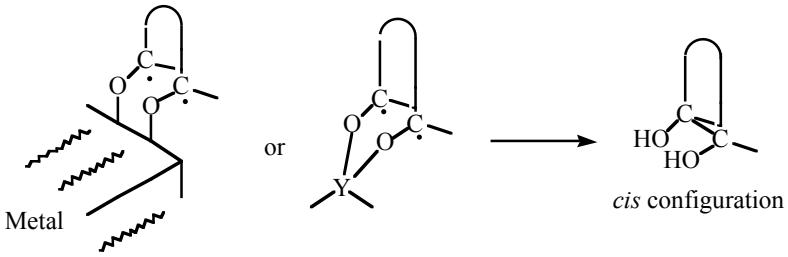
Cpd.	X	Isolated Yield (%) (Recovery of 2a-f (%)) Method A	B	C	D [a)]	mp (˚C)
1a	$-CH_2-$	85 (5)	32 (36)	73 (9)	40 (40)	166-168
1b	$-(CH_2)_2-$	55 (11)	74 (24)	41 (20)	64 (27)	149-151
1c	$-(CH_2)_3-$	62 (4)	77 (6)	60 (6)	59 (26)	180-182
1d	$-(CH_2)_4-$	53 (8)	50 (29)	50 (27)	42 (48)	216-218
1e	$-(CH_2)_2-O-(CH_2)_2-$	39 (2)	41 (10)	47 (7)	49 (18)	176-180
1f	$-(CH_2)_6-$	46 (11)	65 (21)	52 (8)	73 (17)	96-98

a) Method **A**: Zn, 10% NaOH, ultrasonication, 60˚C, 5 h; Method **B**: Al, 10% NaOH, ultrasonication, 60˚C, 5 h; Method **C**: Zn, 10% NaOH, rt, 5 h; Method **D**: Al, 10% NaOH, rt, 5 h.

Although the use of Al powder seems to be more effective in these processes, Zn powder afforded a higher purity of desired cyclic diols. Longer reaction time does not affect overall yield in the case of small rings (**1a-c**), but the transformations are almost quantitative when **1d-f** are obtained in 24 h reactions.

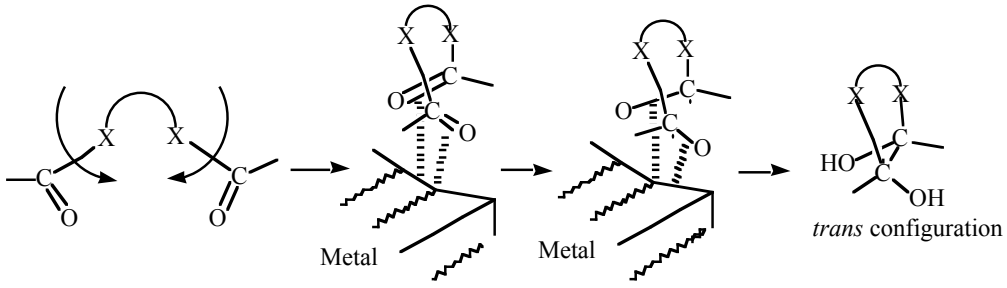
An interesting aspect in the syntheses of diols (**1a-f**) is represented by the fact that only one isomer was formed. On the basis of NMR studies we can assume a *trans* configuration of the central cycle, which is in agreement with previous stereochemical studies that also emphasized the preferential formation of *trans*

structures,[2a,2c,4] exception being made by reductive coupling reactions of aliphatic dialdehydes catalyzed by SmI_2 or Bu_3SnH.[2b,2d,2f] For example, McMurry[2c] showed that for titanium-induced intramolecular pinacolization, the ratio between *cis* and *trans* isomers varies from *cis* as major product to *trans* as major product in direct connection with the size of the ring: small rings prefer a *cis* configuration while larger cyclic compounds adopt a *trans* configuration. Furthermore, most of the reductive coupling reactions were assumed to proceed by the dimerizations of carbonyl radical anions formed by a single electron transfer.[2c] The diradicals can dimerize either on the metal surface or when linked to the complex which catalyzes the reaction (so that steric interactions are minimized):



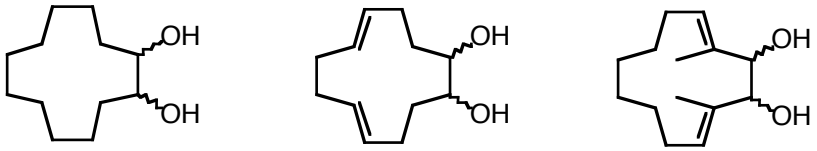
Scheme 4 *McMurry's model for the formation of cis configuration of diols*[2c]

In McMurry's reductive coupling processes or in other such similar processes, the affinity of Ti for oxygen or of SmI_2 for oxygen, respectively, may offer a possible explanation for the mechanism presented in **Scheme 4**. In the case of Zn or Al, the relation between the metal and the oxygen atom or the carbonyl group is not clearly established, but we can suppose that: 1) if the distance between the two carbonyl groups is long enough (at least 8 or 9 atoms, as in the case of aliphatic dialdehydes[2c]), 2) if the molecule presents a rigid system, similar to aromatic aldehydes, and 3) if the chain connecting the two carbonyl groups offers few possibilities of rotation of the molecule, then the approach of the two carbonyl moieties will take place in such a manner that the two carbonyl groups are coming from opposite directions and this will compel the diradical into a conformation in which the two oxygen atoms are in opposite positions, leading finally to a *trans* configuration of the intramolecular reductive coupling product:



Scheme 5 *Proposed model for the formation of trans configurated diols*

Thus, it seems very probable that all our compounds assumed a *trans* configuration due to their aromatic bridged structures. An illustration of such behaviour is the different ratios between *cis* and *trans* isomers obtained in the case of cyclic aliphatic diols **(4**, **5** and **6)**:[2c,2h]



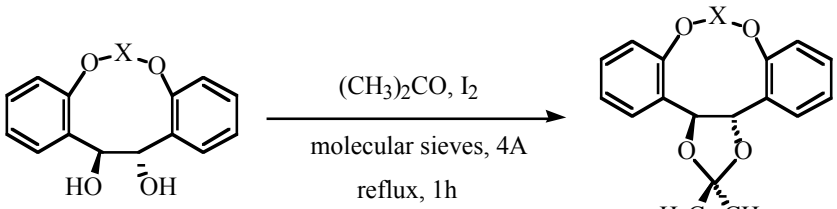
	4	**5**	**6**
cis / trans:	25 : 75	5 : 95	5 : 95

Scheme 6 *cis/trans Ratios for cyclic aliphatic diols (**4-6**)*

As we can see from **Scheme 6**, just by introducing a small restrain such as two double bonds in a 12-atoms chain, the ratio of *cis* / *trans* isomers changed from 25 : 75 to 5 : 95.

On the other hand, the ^{1}H-NMR of the diols **(1a-f)** showed symmetrical aromatic rings (identical signals for all 4 types of aromatic protons – see EXPERIMENTAL) and a single signal for both the CH(OH) methyne groups, although it is splitted in two due to coupling with OH groups (on deuteration, the methyne signal became a sharp singlet). A singlet for both methyne groups means that both groups are equivalent. Getting identical signals for all the 4 types of aromatic protons requires similar environments and this is possible in a *trans* configuration, as suggested also by MM2 and MOPAC calculation and molecule geometry simulation.

In order to establish with great certainty the stereochemistry of each product, we converted the diols into their acetonides:[2h]



1a-f **7 a-f**

Scheme 7 *Transformation into acetonides (**7a-f**) of diols (**1a-f**)*

In all cases, the acetonides showed the -CH(OR)- methine hydrogens as sharp singlet in the range 5.29-5.69 ppm and, most important, the two methyl groups as a singlet between 1.47 and 1.61 ppm. This indicated clearly a *trans* configuration.[2h] In the case of *cis* acetonide the two methyl groups present two different signals.[18]

CONCLUSIONS

We succeeded in the cyclization of dialdehydes by intramolecular reductive coupling processes, in aqueous media and in convenient reaction conditions. Moreover, the reactions presented a very high stereoselectivity, the *trans* isomers being the single reductive coupling products.

ACKNOWLEDGEMENT

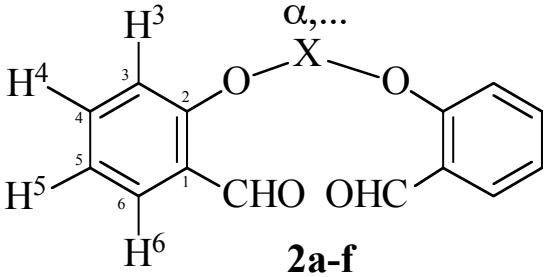
The authors thank Ms. Miho Tamura for performing all elemental analyses.

EXPERIMENTAL

Melting points were determined on a Yanaco Micro Melting Point Apparatus and are uncorrected. All NMR spectra were recorded on a JEOL JNM-LA 300, 300 MHz, in $CDCl_3$ with TMS as internal standard. *J* values are given in Hz. Identification of products in reaction mixtures was made by GC (SHIMADZU GC=17A, carrier gas N_2, pressure 135 Kgf/cm^2, flow 55 mL/min on a J&W Scientific DB-1 fused silica capillary column, length 30 m, I.D. 0.32 mm with film of 0.25 mm) and GC-MS (Hewlett-Packard HP6890 GC, carrier gas He, flow 1.5 mL/min, velocity 48 and pressure 10.3, J&W Scientific DB-1 fused silica capillary column and Jeol - AUTOMASS system II MS). IR spectra were recorded on a JEOL JIR-WINSPEC50 (KBr).

General Procedure for the Synthesis of Dialdehydes (2a-f)

In a 500 mL 3-necked round bottom flask provided with reflux condenser were introduced 12.2 g (0.1 mol) salicylaldehyde in 10 mL of EtOH and 200 mL of 2% aqueous NaOH (0.1 mol NaOH) solution. After 15 min of stirring, a solution of 0.05 mol of the corresponding dibrominated compound disolved in 150 mL of EtOH was added in one portion. The mixture was kept with magnetical stirring, under reflux, for 72 h. The reaction mixture was cooled and kept for 24 h on ice. The dialdehyde slowly precipitated. After filtration and drying, the crude dialdehydes were recrystallized from EtOH or *i*-PrOH.



2a-f

2a: X = -$\overset{\alpha}{C}H_2$-, **2b**: -$\overset{\alpha}{C}H_2$-CH_2-, **2c**: -$\overset{\alpha}{C}H_2$-$\overset{\beta}{C}H_2$-CH_2-,
2d: -$\overset{\alpha}{C}H_2$-$\overset{\beta}{C}H_2$-CH_2-CH_2-, **2e**: -$\overset{\alpha}{C}H_2$-$\overset{\beta}{C}H_2$-O-CH_2-CH_2-
2f: -$\overset{\alpha}{C}H_2$-$\overset{\beta}{C}H_2$-$\overset{\gamma}{C}H_2$-CH_2-CH_2-CH_2-

2,2'-Methylenebis(oxy)bisbenzaldehyde (2a).

This compound was obtained as white needles (*i*-PrOH), mp 131°C (lit.,[13a,14a] 131-2°C).[16] ν (KBr, cm^{-1}): 2863, 2759, 1685, 1596; δ_H: 6.00 (s, 2H$^{\alpha}$), 7.14-7.20 (m, 2H^5, 7.7, 7.5, 0.9), 7.34-7.38 (m, 2H^3, 7.3, 0.9), 7.57-7.64 (ddd, 2H^4, 7.5, 7.3 ,1.9), 7.84-7.88 (dd, 2H^6, 7.7, 1.9), 10.46 (s, 2H, CHO); δ_C: 90.75 (C$^{\alpha}$), 114.93 (2C^3), 123.03 (2C^5), 125.80 (2C^1), 128.97 (2C^6), 135.96 (2C^4), 158.61 (2C^2), 188.96 (2CHO); m/z (intensity): 256 (M$^+$, 1), 135 (M - O-C_6H_4-CHO, 100), 77 (C_6H_5, 32). *Anal.* Calcd for $C_{15}H_{12}O_4$: C, 70.30; H, 4.72. Found: C, 70.26; H, 4.75.

1,2-Bis(2'-formylphenyl)-1,2-dioxaethane (2b).

This compound was obtained as yellow needles (EtOH), mp 130°C (lit.,[13a] 130°C). ν (KBr, cm^{-1}): 2942, 2865, 1685, 1596; δ_H: 4.59 (s, 4H$^{\alpha}$), 7.04-7.12 (m, 2H^5, 2H^3, 8.3, 7.7, 6.6, 0.8), 7.53-7.61 (ddd, 2H^4, 8.3,

6.6, l.9), 7.83-7.87 (dd, $2H^6$, 7.7, 1.9), 10.44 (s, 2H, CHO); δ_C: 67.07 ($2C^{\alpha}$), 112.74 ($2C^3$), 121.52 ($2C^5$), 125.29 ($2C^1$), 128.72 ($2C^6$), 135.87 ($2C^4$), 160.72 ($2C^2$), 188.27 (2CHO); m/z (intensity): 270 (M^+, 2), 149 (M – -O-C_6H_4-CHO, 37), 121 (M – -$(CH_2)_2$-O-C_6H_4-CHO, 100), 77 (C_6H_5, 45). *Anal.* Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.12; H, 5.30.

1,3-Bis(2'-formylphenyl)-1,3-dioxapropane (2c).

This compound was obtained as white needles (EtOH), mp 98°C (lit.,[13a] 97-98°C). ν (KBr, cm^{-1}): 2967, 2869, 2763, 1683, 1600; δ_H: 2.43 (q, $2H^{\beta}$, 6.0), 4.33 (t, $4H^{\alpha}$, 6.0), 6.99-7.07 (m, $2H^5$, $2H^3$, 8.4, 7.7, 7.5, 0.8), 7.51-7.57 (ddd, $2H^4$, 8.4, 7.4, l.6), 7.80-7.85 (dd, $2H^6$, 7.7, 1.6), 10.50 (s, 2H, CHO); δ_C: 29.07 (C^{β}), 64.64 ($2C^{\alpha}$), 112.41 ($2C^3$), 120.95 ($2C^5$), 124.92 ($2C^1$), 128.68 ($2C^6$), 135.96 ($2C^4$), 160.90 ($2C^2$), 189.33 (2CHO); m/z (intensity): 284 (M^+, 2), 163 (M – -O-C_6H_4-CHO, 11), 121 (M – -$(CH_2)_3$-O-C_6H_4-CHO, 100), 77 (C_6H_5, 68). *Anal.* Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found C, 71.72; H, 5.70.

1,4-Bis(2'-formylphenyl)-1,4-dioxabutane (2d).

The compound was obtained as white needles (EtOH), mp 112°C (lit.,[13a] 112.5-113.5°C). ν (KBr, cm^{-1}): 2964, 2877, 1685, 1600; δ_H: 2.11 (t, $4H^{\beta}$, 5.4), 4.19 (t, $4H^{\alpha}$, 5.4), 6.96-7.06 (m, $2H^5$, $2H^3$, 9.1, 8.5, 7.7, 0.9), 7.50-7.57 (ddd, $2H^4$, 9.1, 8.5, l.3), 7.80-7.85 (dd, $2H^6$, 7.7, 1.3), 10.49 (s, 2H, CHO); δ_C: 25.90 ($2C^{\beta}$), 67.88 ($2C^{\alpha}$), 112.40 ($2C^3$), 120.75 ($2C^5$), 124.92 ($2C^1$), 128.50 ($2C^6$), 135.91 ($2C^4$), 161.12 ($2C^2$), 189.46 (2CHO); m/z (intensity) 298 (M^+, 1), 177 (M – -O-C_6H_4-CHO, 5), 158 (M – -$(CH_2)_3$-O-C_6H_4-CHO, 10), 121 (M – -$(CH_2)_4$-O-C_6H_4-CHO, 63), 77 (C_6H_5, 50), 55 (100). *Anal.* Calcd for $C_{18}H_{18}O_4$: C, 72.46; H, 6.07. Found C, 72.41; H, 6.17.

2,2'-Bis(*o*-formylphenyl)-diethyl ether (2e).

This compound was obtained as white needles (EtOH), mp 73.5–75°C (lit.,[15b] 66-7°C). ν (KBr, cm^{-1}): 2937, 2894, 1685, 1600; δ_H: 3.98-4.01 (2d, $4H^{\beta}$, 4.6, 3.3), 4.25-4.29 (2d, $4H^{\alpha}$, 4.6, 3.3), 6.97-7.07 (m, $2H^5$, $2H^3$, 8.3, 7.7, 7.5), 7.50-7.57 (ddd, $2H^4$, 8.3, 7.5, l.9), 7.80-7.85 (dd, $2H^6$, 7.7, 1.9), 10.50 (s, 2H, CHO); δ_C: 68.32 ($2C^{\beta}$), 68.89 ($2C^{\alpha}$), 112.84 ($2C^3$), 121.11 ($2C^5$), 125.13 ($2C^1$), 128.45 ($2C^6$), 135.87 ($2C^4$), 161.06 ($2C^2$), 189.63 (2CHO); m/z (intensity): 314 (M^+. 1), 135 (M – -CH_2-O-$(CH_2)_2$-O-C_6H_4-CHO, 28), 121 (M— -$(CH_2)_2$-O-$(CH_2)_2$-O-C_6H_4-CHO, 66), 77 (C_6H_5, 52), 55 (100). *Anal.* Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. 5.77. Found C, 68.63; H, 5.80.

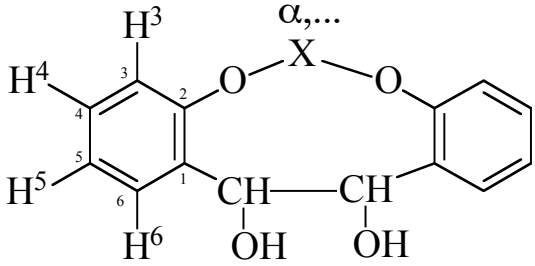
1,6-Bis(2'-formylphenyl)-1,6-dioxahexane (2f).

This compound was obtained as pale yellow needles (EtOH), mp 77-79°C (lit.,[13a] 79.5-80°C). ν (KBr, cm^{-1}): 2931, 2852, 1685, 1675, 1596; δ_H: 1.59 (t, $4H^{\gamma}$, 6.4), 1.90 (q, $4H^{\beta}$, 6.4), 4.10 (t, $4H^{\alpha}$, 6.4), 6.95-7.05 (m, $2H^5$, $2H^3$, 8.4, 7.3, 7.7, 0.8), 7.50-7.57 (ddd, $2H^4$, 8.4, 7.3, l.8), 7.80-7.85 (dd, $2H^6$, 7.7, 1.8), 10.51 (s, 2H, CHO); δ_C: 25.85 ($2C^{\gamma}$), 29.06 ($2C^{\beta}$), 68.29 ($2C^{\alpha}$), 112.49 ($2C^3$), 120.60 ($2C^5$), 124.94 ($2C^1$), 128.34 ($2C^6$), 135.95 ($2C^4$), 161.46 ($2C^2$), 189.80 (2CHO); m/z (intensity) 326 (M^+, 1), 205 (M – -O-C_6H_4-CHO, 3), 121 (M – -$(CH_2)_6$-O-C_6H_4-CHO, 31), 77 (C_6H_5, 29), 55 (100). *Anal.* Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found C, 73.57; H, 6.83.

General Procedure for the Synthesis of Cyclic Diols (1a-f)

Methods A and B: In a 100 mL 3-necked round bottom flask provided with reflux condenser and mechanical stirrer were introduced 2 mmol of dialdehyde in 10 mL of EtOH and 30 mmol of metal (1.95 g Zn or 0.9 g Al). Aqueous NaOH (10%) solution (20 mL, 4 mmol) was added in one portion. The reaction mixture was stirred under ultrasonication, at 60˚C, for 5 h. The metallic residue was filtered off, washed with water and dichloromethane. The filtrate was extracted with dichloromethane (45 mL in 3 portions). The combined organic layers were dried on $MgSO_4$, the solvent evaporated and the crude residue submitted to column chromatography on Wakogel C-300 (silica gel, dimension of particle 45-70 μm, eluent hexane-acetone 100:0 to 70:30).

Methods C and D: In a 100 mL round bottom flask provided with reflux condenser were introduced 2 mmol of dialdehyde in 10 mL of EtOH and 30 mmol of metal (1.95 g Zn or 0.9 g Al). Aqueous NaOH (10%) solution (20 mL, 4 mmol) was added in one portion. The reaction mixture was stirred at rt for 5 h. The metallic residue was filtered off, washed with water and dichloromethane. The filtrate was extracted with dichloromethane (45 mL in 3 portions). The combined organic layers were dried on $MgSO_4$, the solvent evaporated and the crude residue submitted to column chromatography on Wakogel C-300 (silica gel, dimension of particle 45-70 μm, eluent hexane-acetone 100:0 to 70:30).



1a-f

1a: X = -$\overset{\alpha}{C}H_2$-, **1b**: -$\overset{\alpha}{C}H_2$-CH_2-, **1c**: -$\overset{\alpha}{C}H_2$-$\overset{\beta}{C}H_2$-CH_2-,
1d: -$\overset{\alpha}{C}H_2$-$\overset{\beta}{C}H_2$-CH_2-CH_2-, **1e**: -$\overset{\alpha}{C}H_2$-$\overset{\beta}{C}H_2$-O-CH_2-CH_2-
1f: -$\overset{\alpha}{C}H_2$-$\overset{\beta}{C}H_2$-$\overset{\gamma}{C}H_2$-CH_2-CH_2-CH_2-

4,5-Dihydroxy-1,8-dioxy-2,3:6,7-dibenzocyclononane (1a).

This compound was obtained as white prisms, mp 166-168˚C. ν (KBr, cm^{-1}): 3471 (OH, sh), 3357, 3299 (OH, br), 3020, 2937, 2886, 1604; δ_H: 3.07 (d, 2H, OH-exchanges with D_2O, 3.5), 5.45 (s, $2H^{\alpha}$), 5.54 (d, 2H, CH, 3.5), 6.81-6.87 (d, $2H^3$, 7.7), 6.95-7.03 (dd, $2H^5$, 7.5, 7.3), 7.07-7.16 (ddd, $2H^4$, 7.7, 7.3, 1.4), 7.20-7.25 (dd, $2H^6$, 7.5, 1.4); δ_C: 76.61 (2-C(OH)-), 101.01 ($2C^{\alpha}$), 121.23 ($2C^3$), 125.22 ($2C^5$), 129.07 ($2C^6$), 129.67 ($2C^4$), 134.41 ($2C^1$), 155.61 ($2C^2$); m/z (intensity): 258 (M^+, 1), 136 (M – -O-C_6H_4-CH-OH, 100), 122 (M – -CH_2-O-C_6H_4-CH-OH, 35), 105 (M – -O-CH_2-O-C_6H_4-CH-OH, 16), 77 (C_6H_5, 48). *Anal.* Calcd for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found C, 69.82; H, 5.51.

4,5-Dihydroxy-1,8-dioxy-2,3:6,7dibenzocyclodecane (1b).

This compound was obtained as white prisms, mp 149-151˚C. ν (KBr, cm^{-1}): 3403 (OH, sh), 3345 (OH,

br), 2939, 2881, 1600; δ_H: 2.85 (d, 2H, OH-exchanges with D_2O, 2.9), 4.21 (d, $2H^{\alpha}$, 7.0), 4.44 (d, $2H^{\alpha}$, 7.0), 5.39 (d, 2H, CH, 2.9), 6.81-6.85 (dd, $2H^3$, 7.9, 1.1), 6.88-6.94 (ddd, $2H^5$, 7.7, 7.5, l.1), 7.07-7.13 (ddd, $2H^4$, 7.9, 7.7, l.8), 7.21-7.44 (dd, $2H^6$, 7.5, 1.8); δ_C: 70.59 ($2C^{\alpha}$), 75.72 (2C(OH)-), 118.35 ($2C^3$), 123.27 ($2C^5$), 128.82 ($2C^6$), 128.91 ($2C^4$), 133.17 ($2C^1$), 156.04 ($2C^2$); m/z (intensity): 272 (M^+, 3), 149 (M – -HO-C_6H_4-CHOH, 28), 122 (M – -$(CH_2)_2$O-C_6H_4-CHOH, 100), 105 (M – -O-$(CH_2)_2$-O-C_6H_4-CHOH, 22), 77 (C_6H_5, 46). *Anal.* Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found C, 70.46; H, 6.09.

4,5-Dihydroxy-1,8-dioxy-2,3:6,7-dibenzocycloundecane (1c).

This compound was obtained as white prisms, mp 180-182°C. ν (KBr, cm^{-1}): 3469 (OH, sh), 3261 (OH, br), 2942, 2925, 2863, 1602; δ_H: 2.18 (2q superposed, $2H^{\beta}$, 4.6), 2.75 (d, 2H, OH-exchanges with D_2O, 6.7), 4.13 (2t superposed, $2H^{\alpha}$, 4.6), 4.33 (2t superposed, $2H^{\alpha}$, 6.0), 5.27 (d, 2H, CH, 6.7), 7.00-7.10 (m, $2H^5$, $2H^3$, 7.8, 7.6, 7.5, 1.1), 7.20-7.27 (ddd, $2H^4$, 7.8, 7.5, l.6), 7.45-7.50 (dd, $2H^6$, 7.6, 1.6); δ_C: 28.93 (C^{β}), 69.04 ($2C^{\alpha}$), 71.81 (2-C(OH)-), 117.13 ($2C^3$), 122.68 ($2C^5$), 126.64 ($2C^6$), 128.38 ($2C^4$), 134.26 ($2C^1$), 155.59 ($2C^2$); m/z (intensity): 286 (M^+, 4), 165 (M – -O-C_6H_4-CHOH, 16), 135 (M – -$(CH_2)_2$-O-C_6H_4-CHOH, 36), 121 (M – -$(CH_2)_3$-O-C_6H_4-CHOH, 100), 105 (M – -O-$(CH_2)_3$-O-C_6H_4-CHOH, 56), 77 (C_6H_5, 99). *Anal.* Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found C, 71.30; H, 6.47.

4,5-Dihydroxy-1,8-dioxy-2,3:6,7-dibenzocyclododecane (1d).

This compound was obtained as white prisms, mp 216-218°C. ν (KBr, cm^{-1}): 3490 (OH, sh), 3351 (OH, br), 2929, 2892, 2842, 1600; δ_H: 2.01-2.12 (m, $4H^{\beta}$), 2.42 (d, 2H, OH -exchanges with D_2O, 6.8), 3.99-4.09 (m, $4H^{\alpha}$), 5.42 (d, 2H, CH, 6.8), 6.82-6.87 (dd, $2H^3$, 8.1, 0.7), 6.98-7.05 (ddd, $2H^5$, 7.4, 7.3, 0.7), 7.23-7.30 (ddd, $2H^4$, 8.1, 7.3, l.6), 7.49-7.54 (dd, $2H^6$, 7.4, 1.6); δ_C: 27.37 ($2C^{\beta}$), 68.24 ($2C^{\alpha}$), 70.53 (2-C(OH)-), 110.36 ($2C^3$), 120.19 ($2C^5$), 126.00 ($2C^6$), 128.13 ($2C^4$), 130.99 ($2C^1$), 155.87 ($2C^2$); m/z (intensity): 300 (M^+, 5), 179 (M – -O-C_6H_4-CHOH, 10), 165 (M – -CH_2-O-C_6H_4-CHOH, 8), 135 (M – -$(CH_2)_3$-O-C_6H_4-CHOH, 17), 105 (M – -O-$(CH_2)_4$-O-C_6H_4-CHOH, 22), 77 (C_6H_5, 69), 55 (100). *Anal.* Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found C, 71.77; H, 7.00.

4,5-Dihydroxy-1,8,11-trioxy-2,3:6,7-dibenzocyclotridecane (1e).

This compound was obtained as white prisms, mp 176-180°C. ν (KBr, cm^{-1}): 3531 (OH, sh), 3397 (OH, br), 2923, 2879, 1600; δ_H: 2.61 (d, 2H, OH - exchanges with D_2O, 5.5), 3.88-4.08 (m, $4H^{\beta}$, $2H^{\alpha}$), 4.15-4.22 (m, $2H^{\alpha}$), 5.36 (d, 2H, CH, 5.5), 6.84-6.88 (dd, $2H^3$, 8.3, 1.0), 6.95-7.02 (ddd, $2H^5$, 7.5, 7.5, 1.0), 7.19-7.26 (ddd, $2H^4$, 8.3, 7.5, l.7), 7.44-7.48 (dd, $2H^6$, 7.5, 1.7); δ_C: 68.18 ($2C^{\beta}$), 70.38 ($2C^{\alpha}$), 71.46 (2-C(OH)-), 112.42 ($2C^3$), 121.08 ($2C^5$), 127.53 ($2C^6$), 128.32 ($2C^4$), 130.11 ($2C^1$), 155.56 ($2C^2$); m/z (intensity): 316 (M^+, 3), 165 (M – -$(CH_2)_2$O-C_6H_4-CHOH, 25), 121 (M – -$(CH_2)_2$O$(CH_2)_2$O-C_6H_4-CHOH, 100), 77 (C_6H_5, 55). *Anal.* Calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found C, 67.96; H, 6.49.

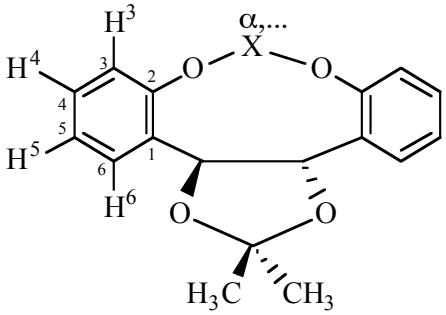
4,5-Dihydroxy-1,8-dioxy-2,3:6,7-dibenzocyclotetradecane (1f).

This compound was obtained as white prisms, mp 96-98°C. ν (KBr, cm^{-1}): 3559 (OH, sh), 3384 (OH, br), 2938, 2862, 2824, 1595; δ_H: 1.76-1.80 (m, $4H^{\gamma}$), 1.82-1.92 (m, $4H^{\beta}$), 2.18 (d, 2H, OH, exchanges with D_2O, 3.8), 4.02-4.08 (m, $4H^{\alpha}$), 5.43 (d, 2H, CH, 3.8), 6.85-6.87 (dd, $2H^3$, 8.0, 0.8), 6.96-7.03 (ddd, $2H^5$, 7.7,

7.5, 0.8), 7.22-7.29 (ddd, $2H^4$, 8.0, 7.5, l.7), 7.56-7.61 (dd, $2H^6$, 7.7, 1.7); δ_C: 26.01 ($2C^{\gamma}$), 26.95 ($2C^{\beta}$), 68.24 ($2C^{\alpha}$), 70.32 (2 -C(OH)-), 110.84 ($2C^3$), 120.43 ($2C^5$), 128.11 ($2C^6$), 128.35 ($2C^1$), 128.73 ($2C^4$), 156.00 ($2C^2$); m/z (intensity): 328 (M^+, 3), 310 ($M^+ - H_2O$, 5), 175 (M – -$(CH_2)_2$-O-C_6H_4-CH-OH, 44), 152 (M – -$(CH_2)_4$-O-C_6H_4-CH-OH, 13), 121 (M – -$(CH_2)_6$-O-C_6H_4-CH-OH, 58), 107 (M – -O-$(CH_2)_6$-O-C_6H_4-CH-OH, 82), 77 (C_6H_5, 59), 55 (100). *Anal.* Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.36. Found C, 73.02; H, 7.45.

***General Procedure for the Preparation of Acetonides (7a-f) Using Acetone / Iodine / Molecular sieves*[19]**

To a solution of diol (0.2 mmol) in acetone (10 mL, pre-dried) placed in a 20 mL two-necked round-bottom flask provided with reflux condenser were added 1.5 g molecular sieves, 4A, previously activated during 4 h at 100˚C. After being stirred for 5 min, 30 mg (0.12 mmol) iodine was added to the mixture. The mixture was heated to reflux with stirring for 1 h. After being cooled to rt, ether (20 mL) was added to the resulting mixture, which was filtered. The filtrate was washed twice with 10% aqueous Na_2SO_3 sol., twice with water and with brine. The organic layer was dried over $MgSO_4$ and then concentrated in vacuo. The crude residue was directly submitted to NMR analysis.



7a-f

7a: X = $\overset{\alpha}{-CH_2-}$, **7b**: $\overset{\alpha}{-CH_2-CH_2-}$, **7c**: $\overset{\alpha}{-CH_2}\overset{\beta}{-CH_2-CH_2-}$,

7d: $\overset{\alpha}{-CH_2}\overset{\beta}{-CH_2-CH_2-CH_2-}$, **7e**: $\overset{\alpha}{-CH_2}\overset{\beta}{-CH_2}$-O-$CH_2$-$CH_2$-

7f: $\overset{\alpha}{-CH_2}\overset{\beta}{-CH_2}\overset{\gamma}{-CH_2-CH_2-CH_2-CH_2-}$

4,5-Dihydroxy-1,8-dioxy-2,3:6,7-dibenzocyclononane acetonide (7a).

δ_H: 1.60 (s, 6H, CH_3), 5.17 (s, 2H, CH), 5.45 (s, $2H^{\alpha}$), 6.89-6.92 (m, $2H^3$), 6.99-7.31 (m, $2H^5$, $2H^4$), 7.66-7.70 (m, $2H^6$)

4,5-Dihydroxy-1,8-dioxy-2,3:6,7-dibenzocyclodecane acetonide (7b).

δ_H: 1.51 (s, 6H, CH_3), 4.16 (d, $2H^{\alpha}$, 7.0), 4.38 (d, $2H^{\alpha}$, 7.0), 5.29 (s, 2H, CH), 6.89-6.92 (m, $2H^3$), 7.01-7.06 (m, $2H^5$), 7.16-7.22 (m, $2H^4$), 7.56-7.59 (m, $2H^6$)

4,5-Dihydroxy-1,8-dioxy-2,3:6,7-dibenzocycloundecane acetonide (7c).

δ_H: 1.47 (s, 6H, CH_3), 1.89-1.92 (m, $2H^{\beta}$), 4.07-4.15 (m, $2H^{\alpha}$), 4.32-4.38 (m, $2H^{\alpha}$), 5.36 (s, 2H, CH), 6.82-6.85 (m, $2H^5$), 6.92-6.97 (m, $2H^3$), 7.14-7.19 (m, $2H^4$), 7.53-7.57 (m, $2H^6$)

4,5-Dihydroxy-1,8-dioxy-2,3:6,7-dibenzocyclododecane acetonide (7d).

δ_H: 1.55 (s, 6H, CH_3), 1.85-2.09 (m, $4H^{\beta}$), 3.91-4.08 (m, $4H^{\alpha}$), 5.51 (s, 2H, CH), 6.72-6.95 (m, $2H^3$, $2H^5$), 7.08-7.26 (m, $2H^4$), 7.40-7.45 (m, $2H^6$)

4,5-Dihydroxy-1,8,11-trioxy-2,3:6,7-dibenzocyclotridecane acetonide (7e).

δ_H: 1.54 (s, 6H, CH_3), 3.65-3.75 (m, 4H), 4.00-4.13 (m, 4H), 5.69 (s, 2H, CH), 6.79-6.90 (m, $2H^3$, $2H^5$), 7.11-7.18 (m, $2H^4$), 7.32-7.35 (m, $2H^6$)

4,5-Dihydroxy-1,8-dioxy-2,3:6,7-dibenzocyclotetradecane acetonide (7f).

δ_H: 1.56 (s, 6H, CH_3), 1.53-1.80 (m, 4H$^{\gamma}$, 4H$^{\beta}$), 3.88-4.10 (m, 4H$^{\alpha}$), 5.62 (s, 2H, CH), 6.70-6.94 (m, 2H^3, 2H^5), 7.07-7.53 (m, 2H^4, 2H^6)

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16 L. F. Lindoy[14a] reported mp 124˚C, but the dialdehyde seemed to be a crude reaction product; R. Jaunin[13a] reported a recrystallized product of mp 131-132˚C.

17 J. Tirado-Rives[15b] reported a melting point of a crude reaction product.

18 When performing the synthesis of diols **(1b** and **1e)** using SmI_2 in dry THF,[2b] the mixture of *cis* and *trans* configurations for the corresponding diols were obtained. After chromatographic separation and acetonidation, the *cis* diol acetonide presented two distinct signals for the two methyl groups at 1.60 and 1.80 ppm – T. Kawaji, unpublished results

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