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Double Wittig Reactions with 4-Carboxybutylidene Triphenylphosphorane as the Key Step in the Synthesis of Benzene Derivatives Metadisubstituted with ωω'-Difunctionalized Six-Carbon Chains.

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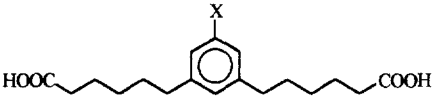
Abstract : Using a double Wittig reaction from diformylbenzene derivatives, a direct synthetic way to 1,3-di(5-carboxypent-1-yl)benzene compounds is discussed.

Symmetrically metadisubstituted benzenic compounds with fonctionnalities in the terminal positions of relatively long chains are interesting synthons in macrocyclic chemistry [1,2]. The diacid derivatives may also be used as particular amphiphiles. In the target molecules described in this paper, the two carboxylic groups are separated by a 13 carbon chain.

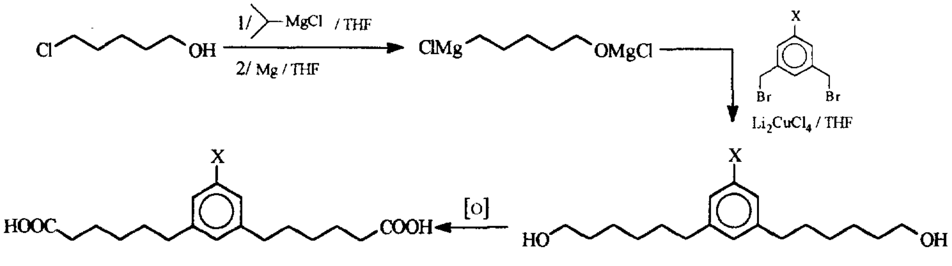


X : H, OMe, OH, OMOM

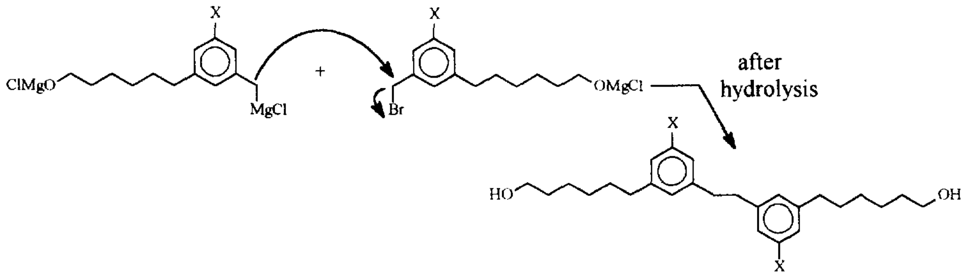
Similar compounds, with shorter lateral chains (3 and 4 carbons) have been obtained by step to step synthesis [1,2].

We describe herein a synthetic way starting from the 1,3-diformylbenzene and branching two lateral long chains in a one step procedure.

Previously, we had investigated the synthetic pathway depicted in scheme 1. This route used the ω-alcoolate Grignard reagents of Normant and al [3]. Unfortunately, an halogen metal exchange reaction (Scheme 2) led to a 1,2-diaryl product instead of the expected one (numerous experimental modifications were unsuccessful and all the reactions gave the same product).

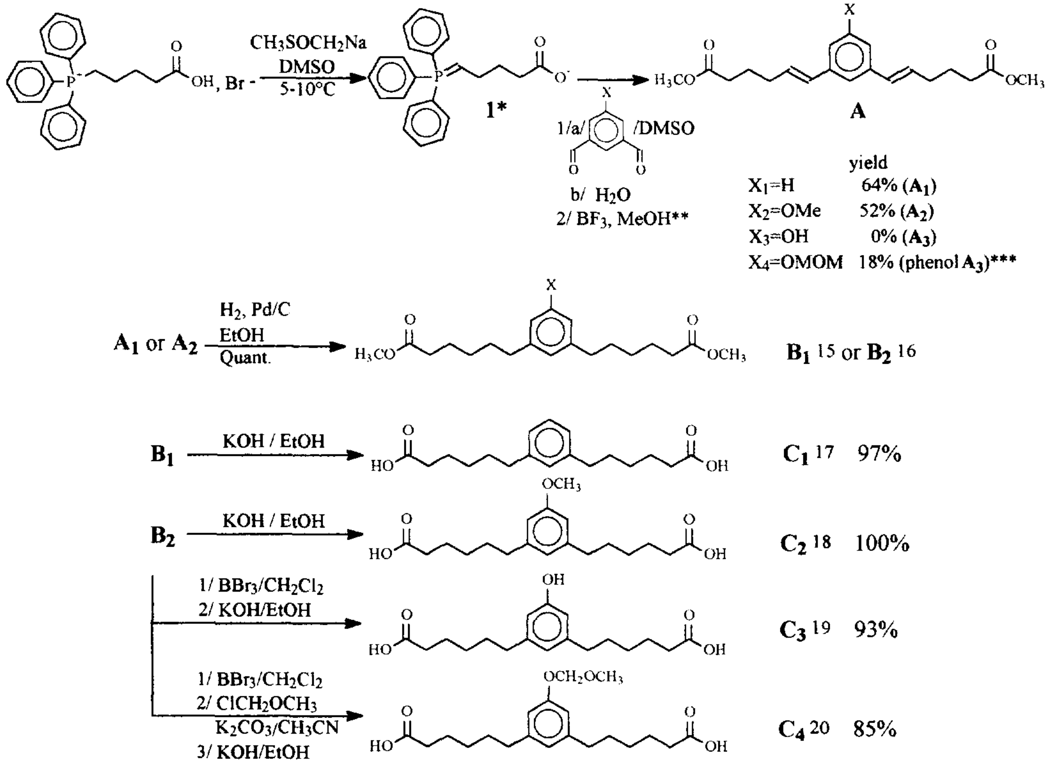


Scheme 1 : Expected reaction pathway.



Scheme 2 : Experimental result.

The second synthetic pathway implied a double Wittig reaction of the ylide **1**, prepared from the 4-carboxybutyltriphenylphosphonium bromide, with the adequate 1,3-diformylbenzene (Scheme 3). When using the phosphonium bromide of the valeric ester, an intramolecular cyclisation of the corresponding ylide occured giving a non reactive cyclopentanone phosphorane derivative[4]. Diacids **C** were obtained from **A** via a sequence of good yield reactions (Scheme 3).



* Ylide **1** has already been successfully used in simple Wittig reactions[5,6,7].

** The crude reaction mixture was esterified for better separation conditions.

*** The phenol group is deprotected during esterification.

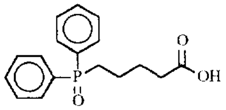
Scheme 3.

When X = OH or OMOM, the corresponding compounds **A** were obtained in very poor yields. However, diacids $\mathbf{C_3}$ and $\mathbf{C_4}$ were easily synthetised from the diester $\mathbf{B_2}$ (Scheme 3).

Otherwise, yields were good and a by-product **2**, identified[21] as the 4-carboxybutyldiphenylphosphine oxide, was isolated in a very small amount. When the exothermic Wittig reaction was not well controlled, **2** became the major reaction product.

According to ^1H and ^{13}C NMR studies, the simultaneous formation of **2** and benzene was observed before final hydrolysis. When reaction is performed in DMSO-d_6 as solvent, the by-product **2** was monodeuteriated on the phosphorous adjacent carbon. This may be explained by a reverse basic attack of the DMSO by the ylide.

(2)



Experimental part :

- Typical procedure for the double Wittig reactions :

Sodium hydride (0.11 mole) free from mineral oil and freshly distilled DMSO (60 ml) were introduced under argon in a three-necked flask fitted with a reflux condenser. The mixture was heated until no more hydrogen evolution and cooled to 5-10°C. Then 49.5 mmoles (22.0 g) of 4-carboxybutyl triphenylphosphonium bromide[8] in 40 ml of DMSO were added. The resulting red solution was stirred at room temperature for 10 min. and 22.4 mmoles (3.0 g) of 1,3-diformylbenzene in 30 ml of DMSO were rapidly added. The resulting solution was stirred for 2 hours at room temperature and then 100 ml of a water/Et_2O (1:1, v/v) mixture was added. The solution was decanted and the aqueous phase was then extracted 2 times with 75 ml of ethyl acetate. The aqueous phase was acidified (pH=1-2) with HCl (37%) and then extracted 3 times with 75 ml of ethyl acetate. This organic layer was washed with brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude mixture (yellow oil) was esterified by refluxing with the BF_3,MeOH complex. Purification by chromatography through silicagel (CH_2Cl_2/ethyl acetate) yielded 4.70 g of $\mathbf{A_1}$[13] as a yellow oil (64%).

Experimental procedures for $\mathbf{A_2}$[14], $\mathbf{A_3}$ and $\mathbf{A_4}$ were the same as the one above mentioned, starting respectively from 5-methoxy-1,3-diformylbenzene[9], 5-hydroxy-1,3-diformylbenzene[10] and 5-(1,3-dioxabutyl)-1,3-diformylbenzene[11].

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8. 4-carboxybutyltriphenylphosphonium bromide was prepared by refluxing 5-bromovaleric acid and triphenyl phosphine in acetonitrile.
9. 5-methoxy-1,3-diformylbenzene was obtained by oxidation (MnO_2/THF) of 5-methoxy-1,3-dihydroxymethylbenzene[12].
10. 5-hydroxy-1,3-diformylbenzene was obtained in three steps [(i) BF_3/MeOH, reflux ; (ii) $LiAlH_4$/THF, reflux ; (iii) MnO_2/THF, reflux] from 5-hydroxy isophtalic acid.
11. 5-(1,3-dioxabutyl)-1,3-diformylbenzene was obtained by reaction of 5-hydroxy-1,3-diformylbenzene[10] with chloromethyl-methylether/K_2CO_3 in acetone.
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13. **A_1 :1,3-di(methanoyloxypent-1-enyl)benzene : M.S.** (FAB+, NBA) : 331 (M) ; 299 (M-MeO) ; 267(M-2 MeO-1). **^{1}H NMR** (200 MHz, $CDCl_3$) ppm : 1.80 (4H, m, $C\underline{H}_2$: β from CO_2Me), 2.19-2.42 (8H, m, $C\underline{H}_2$: α from both CO_2Me and CH=CH), 3.62 and 3.65 (6H, 2s, $CO_2C\underline{H}_3$), 5.55-5.69 and 6.12-6.48 (4H, 3m, $C\underline{H}=C\underline{H}$), 7.08-7.30 (4H, m, $C\underline{H}ar$). **^{13}C NMR** (50 MHz, $CDCl_3$) ppm : 24.3, 24.9, 27.8, 32.2, 33.2, 33.3 (6 $\underline{C}H_2$), 51.3 ($CO_2\underline{C}H_3$), 124.1-128.9 ($\underline{C}Har$), 129.5, 129.6, 130.6, 131.5 ($\underline{C}H=\underline{C}H$), 137.5 ($\underline{C}ar$), 173.7 et 173.8 ($\underline{C}O_2Me$). **Anal.** calc. for $C_{20}H_{26}O_4$: C=72.70% H=7.93% ; found : C=72.43% H=8.04%.
14. **A_2 : 1,3-di(methanoyloxypent-1-enyl)-5-methoxybenzene : M.S.** (FAB+, NBA) : 360 (M) ; 329 (M - OMe). **^{1}H NMR** (200 MHz, $CDCl_3$) ppm : 1.70-1.89 (4H, m, $C\underline{H}_2$: β from CO_2Me), 2.19-2.43 (8H, m, $C\underline{H}_2$: α from both CO_2Me and CH=CH), 3.63-3.66 (6H, 2s, $CO_2C\underline{H}_3$), 3.80 (3H, s, Ar-O-$C\underline{H}_3$), 5.55-5.69 and 6.12-6.45 (4H, 3m, $C\underline{H}=C\underline{H}$), 6.65-6.91 (3H, m, $C\underline{H}ar$). **^{13}C NMR** (50 MHz, $CDCl_3$) ppm : 24.3, 24.9, 27.8, 32.1, 33.2, 33.3 (6 $C\underline{H}_2$), 51.3 ($CO_2\underline{C}H_3$), 55.0 (Ar-O-$\underline{C}H_3$), 109.3, 110.0, 112.4, 113.0, 116.7, 119.3, 121.7 ($\underline{C}Har$), 129.5, 129.8, 130.5, 131.8 ($\underline{C}H=\underline{C}H$), 138.3, 138.6, 138.7, 138.9 ($\underline{C}ar$-CH=CH-), 159.1, 159.5, 159.8 ($\underline{C}ar$-O-Me), 173.7 et 173.8 ($\underline{C}O_2CH_3$). **Anal.** calc. for $C_{21}H_{28}O_5.1/8H_2O$: C=69.54% H=7.85% ; found : C=69.65% H=7.58%.
15. **B_1 : 1,3-di(5-methanoyloxypent-1-yl)benzene : M.S.** (FAB+, NBA) : 331 (M); 303 (M-MeO) ; 271(M-2 MeO-1). **^{1}H NMR** (200 MHz, $CDCl_3$) ppm : 1.35-1.43 (4H, m, $C\underline{H}_2$: γ from CO_2Me), 1.55-1.70 (8H, m, $C\underline{H}_2$: β from both CO_2Me and Ar), 2.30 (4H, t, J=7.6 Hz, $C\underline{H}_2$: α from CO_2Me), 2.58 (4H, t, J=7.6 Hz, $C\underline{H}_2$: α from Ar), 3.65 (6H, s, $CO_2C\underline{H}_3$), 6.96-6.99 (3H, m, 3$C\underline{H}ar$), 7.13-7.17 (1H, m, $C\underline{H}ar$). **^{13}C NMR** (50 MHz, $CDCl_3$) ppm : 24.7, 28.7, 31.0, 33.9, 35.6 (10 $\underline{C}H_2$), 51.3 ($CO_2\underline{C}H_3$), 125.6 (2$\underline{C}Har$), 128.0 and 128.4 (2$\underline{C}Har$), 142.3 ($\underline{C}ar$-CH_2), 174.0 ($\underline{C}O_2Me$). **Anal.** calc. for $C_{20}H_{30}O_4.1/8H_2O$: C=71.34% H=9.06% ; found : C=71.27% H=8.98%.
16. **B_2 : 1,3-di(5-methanoyloxypent-1-yl)-5-methoxybenzene : M.S.** (FAB+, NBA) : 364 (M) ; 333 (M - OMe) ; 301 (M - 2 OMe). **^{1}H NMR** (200MHz, $CDCl_3$) ppm : 1.31-1.43 (4H, m, $C\underline{H}_2$: γ from CO_2Me), 1.58-1.70 (8H, m, $C\underline{H}_2$: β from both CO_2Me and Ar), 2.31 (4H, t, J=7.5 Hz, $C\underline{H}_2$: α from CO_2Me), 2.55 (4H, t, J=7.5 Hz, $C\underline{H}_2$: α from Ar), 3.66 (6H, s, $CO_2C\underline{H}_3$), 3.78 (3H, s, Ar-O-$C\underline{H}_3$), 6.54 (2H, s, $C\underline{H}ar$), 6.58 (1H, s, $C\underline{H}ar$). **^{13}C NMR** (50MHz, $CDCl_3$) ppm : 24.7, 28.7, 30.9, 33.9, 35.7 (10 $\underline{C}H_2$), 51.3 ($CO_2\underline{C}H_3$), 55.0 (Ar-O-$\underline{C}H_3$), 111.1 (2 $\underline{C}Har$), 120.9 (1 $\underline{C}Har$), 143.8 ($\underline{C}ar$-CH_2), 159.5 ($\underline{C}ar$-OMe), 174.1 ($\underline{C}O_2CH_3$). **Anal.** calc. for $C_{21}H_{32}O_5.1/4H_2O$: C=68.36% H=8.87% ; found : C=68.27% H=8.77%.
17. **C_1 : 1,3-di(5-carboxypent-1-yl)benzene : mp :** 81-81.5°C. **S.M.** (C.I.) : 307(M+1) ; 289(M-OH+1). **^{1}H NMR** (200 MHz, $CDCl_3$) ppm : 1.33-1.45 (4H, m, $C\underline{H}_2$: γ from CO_2Me), 1.55-1.70 (8H, m, $C\underline{H}_2$: β from both CO_2Me and Ar), 2.35 (4H, t, J=7.3 Hz, $C\underline{H}_2$: α from CO_2H), 2.58 (4H, t, J=7.5 Hz, $C\underline{H}_2$: α from Ar), 6.96-6.99 (3H, m, $C\underline{H}ar$), 7.14-7.25 (1H, m, $C\underline{H}ar$), 11.30 (2H, s, $CO_2\underline{H}$). **^{13}C NMR** (50 MHz, $CDCl_3$) ppm : 24.5, 28.6, 31.0, 34.0, 35.6 (10 $\underline{C}H_2$), 125.7 (2$\underline{C}Har$), 128.2 and 128.5 (2CHar), 142.4 (Car-CH_2), 180.3 ($\underline{C}O_2H$). **Anal.** calc. for $C_{18}H_{26}O_4$: C=70.56% H=8.55% ; found C=70.15% H=8.55%.
18. **C_2 : 1,3-di(5-carboxypent-1-yl)-5-methoxybenzene : m.p. :** 55-55.5°C. **M.S.** (FAB-, NBA) : 335 (M-1) ; 305 (M - OMe) ; (FAB+, NBA) : 336 (M). **^{1}H NMR** (200MHz, $CDCl_3$) ppm : 1.30-1.50 (4H, m, $C\underline{H}_2$: γ from CO_2H), 1.55-1.80 (8H, m, $C\underline{H}_2$: β from both CO_2Me and Ar), 2.35 (4H, t, J=7.3 Hz, $C\underline{H}_2$: α from CO_2H), 2.56 (4H, t, J=7.5 Hz, $C\underline{H}_2$: α from Ar), 3.78 (3H, s, Ar-O-$C\underline{H}_3$), 6.54 (2H, s, $C\underline{H}ar$), 6.58 (1H, s, $C\underline{H}ar$), 9.80 (2H, $CO_2\underline{H}$). **^{13}C NMR** (50MHz, $CDCl_3$) ppm : 24.5, 28.7, 30.9, 34.0 et 35.7 (10 $\underline{C}H_2$), 55.1 (Ar-O-$\underline{C}H_3$), 111.3 (2 $\underline{C}Har$), 121.0 (1 $\underline{C}Har$), 143.8 (2 $\underline{C}ar$-CH_2-), 159.6 ($\underline{C}ar$-OMe), 180.3 ($\underline{C}O_2H$). **Anal.** calc. for $C_{19}H_{28}O_5.1/2H_2O$: C=66.06% H=8.46% ; found C=66.43% H=8.21%.
19. **C_3 : 1,3-di(5-carboxypent-1-yl)-5-hydroxybenzene : m.p. :** 89-90°C. **M.S.** (DCI ; NH_3, isobutane) : 322 (M) ; 305(M-OH) ; 287 (M-2OH-1). **^{1}H NMR** (200MHz, $CDCl_3$) ppm : 1.29-1.43 (4H, m, $C\underline{H}_2$: γ from CO_2H), 1.52-1.73 (8H, m, $C\underline{H}_2$: β from both CO_2H and Ar), 2.30 (4H, t, J=7.4 Hz, $C\underline{H}_2$: α from CO_2H), 2.50 (4H, t, $C\underline{H}_2$: α from Ar), 3.67 (6H, s, $CO_2C\underline{H}_3$), 6.48 (3H, s, $C\underline{H}ar$), 8.00-9.60 (3H, $CO_2\underline{H}$ et Ar-O$\underline{H}$). **^{13}C NMR** (50MHz, $CDCl_3$) ppm : 24.5, 28.6, 30.8, 33.9, 35.4 (10 $\underline{C}H_2$), 112.7 (2 $\underline{C}Har$), 120.0 (1 $\underline{C}Har$), 143.7 ($\underline{C}ar$-CH_2-), 156.5 ($\underline{C}ar$-OH), 177.1 ($\underline{C}O_2CH_3$).
20. **C_4 : 1,3-di(5-carboxypent-1-yl)-5-(1,3-dioxabutyl)benzene : M.S.** (DCI ; NH_3/isobutane) : 384 (M + NH_3 +1) ; 366 (M) ; 335 (M - OMe) ; 317 (M - OMe - OH - 1) ; 305 (M - CH_2OCH_3 - OH +1) ; 285 (M - CH_2OCH_3 - OH -2). **^{1}H NMR** (200 MHz, $CDCl_3$) ppm : 1.33-1.48 (4H, m, $C\underline{H}_2$: γ from CO_2H), 1.56-1.75 (8H, m, $C\underline{H}_2$: β from both CO_2H and Ar), 2.31 (4H, t, $C\underline{H}_2$: α from CO_2H), 2.55 (4H, t, $C\underline{H}_2$: α from Ar), 3.48 (3H, s, $C\underline{H}_3$-O-CH_2), 5.15 (2H, s, CH_3-O-$C\underline{H}_2$-O), 6.64 (1H, s, $C\underline{H}ar$), 6.67 (2H, s, $C\underline{H}ar$). **^{13}C NMR** (50 MHz, $CDCl_3$) ppm : 24.4, 28.6, 30.8, 33.9, 35.6 (10 $\underline{C}H_2$), 55.8 ($\underline{C}H_3$-O-CH_2), 94.3 (CH_3-O-$\underline{C}H_2$-O), 113.5 (2 $\underline{C}Har$), 122.2 (1 $\underline{C}Har$), 143.8 ($\underline{C}ar$-CH_2-), 157.2 ($\underline{C}ar$-OH), 180.2 ($\underline{C}O_2H$).
21. **Characterisation of the by-product 3 : 4-carboxybutyldiphenylphosphine oxide : m.p. :** 103°C. **M.S.** (DCI ; NH_3/isobutane) : 317 (M + 1). **^{1}H NMR** (200 MHz, $CDCl_3$) ppm : 1.55-1.85 (4H, m, $C\underline{H}_2$: β from both CO_2H and P=O), 2.25-2.42 (4H, m, $C\underline{H}_2$: α from both CO_2H and P=O), 7.40-7.54 (6H, m, $C\underline{H}ar$), 7.65-7.80 (4H, m, $C\underline{H}ar$), 8.1-8.8 (1H, CO_2H). **^{13}C NMR** (50 MHz, $CDCl_3$) ppm : 20.9 ($\underline{C}H_2$: β from P=O), 26.1 ($\underline{C}H_2$: β from CO_2H, $J_{C\text{-}P}$ = 14.9 Hz), 29.1 ($\underline{C}H_2$: α from P=O, $J_{C\text{-}P}$ = 71.1 Hz), 33.7 ($\underline{C}H_2$: α from CO_2H), 128.7 ($\underline{C}Har$, J=11.7 Hz), 130.7 ($\underline{C}Har$, J=9.4 Hz), 131.9 ($\underline{C}Har$), 132.3 ($\underline{C}Har$), 175.8 ($\underline{C}O_2H$).

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