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Selective Enzymatic Hydrolysis of (*Z,E*)-Dimethyl-2,4-Hexadienedioate. Preparation of (*Z,E*)Difunctionalized Dienes

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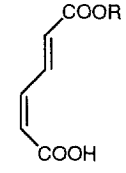
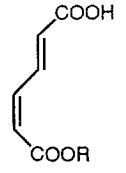
Key words : (*Z,E*)-Muconic acid monoesters, (*Z,E*) dienes, *Pig Liver Esterase*, enzymatic hydrolysis, selective reduction.

Abstract : Enzymatic hydrolysis of (*Z,E*)-dimethyl-2,4-hexadienedioate **6** by *Pig Liver Esterase* mainly led to (2*E*,4*Z*)-5-methoxycarbonyl-2,4-pentadienoic acid **2a**. This compound was a starting material for the preparation of other difunctionalized dienes.

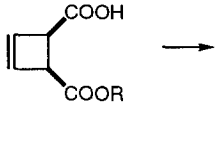
Monoprotected derivatives of (*Z,E*)-muconic acid **1** and **2** are interesting synthetic intermediates in synthesis of macrocyclic trichothecenes.[1-5] Preparation of these compounds was possible in several ways. For instance the oxidative cleavage of catechol in the presence of methanol led to (*Z,Z*)-monomethyl muconate[6] which was converted into the isomerisation product **1a**.[7,8] Preparation of compounds **1b** and **1c** also involved the oxidative cleavage of catechol.[7]



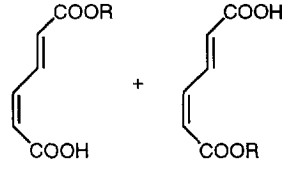
1a R = Me[7,8]
1b R = CH_2-CH_2-SMe[7]
1c R = CH_2-CH_2-$SiMe_3$[1,7]
1d R = CH_2-C_6H_4-*p*OMe[4]



2b R = CH_2-CH_2-SMe[7]
2c R = CH_2-CH_2-$SiMe_3$[4]



3a R = Me
3c R = CH_2-CH_2-$SiMe_3$
3e R = (2-naph)
3f R = *n*Bu

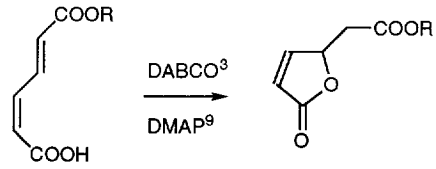


1a	2:1[9]	**2a**
1c	1.2:1 to 3:1[3]	**2c**
1e	2:1[9]	**2e**
1f	1.2:1 to 3:1[3]	**2f**

On the other hand compounds **1c**[1] and **1d**[4] could be prepared by Wittig[1] or Horner-Emmons[4] reactions with malealdehydic acid.

Several (2*Z*,4*E*)-monoesters **1** (e.g. **1c** and **1d**) were esterified and the corresponding diesters were selectively cleaved leading to (2*E*,4*Z*)-monoesters **2** (**2b**[7] and **2c**,[4] respectively).

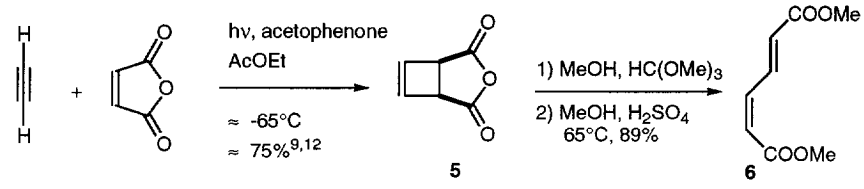
The cyclobutene thermolysis method is another interesting way[3,9] for obtention of compounds **1** and **2**. It leads either to the same amounts of both isomers or to an excess of isomer **1** depending on the sarting material and on the experimental conditions. Isomer **2** could be separated from the **1** + **2** mixture by the facile base-catalysed cyclisation of isomer **1** leading to lactone **4**.[3,9]



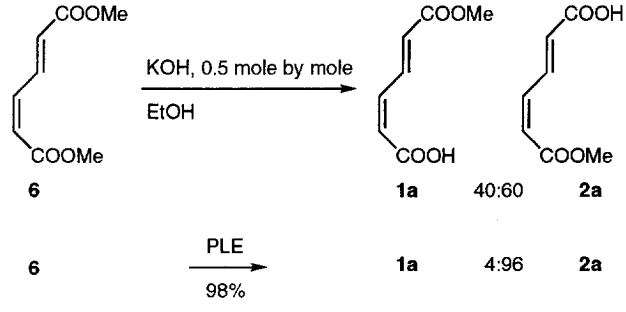
1 **4**

Therefore there are specific methods for preparation of compounds **1** whereas obtention of their isomers **2** involves either a two step sequence from **1** or isolation of **2** from an **1** + **2** mixture in which the amount of **2** is ≤ 50%. (for another preparation of **1a** see ref 10).

We tried to circumvent these difficulties in obtention of compounds such as **2a** through the selective hydrolysis of the corresponding diester **6**.[11] We prepared this compound **6** *via* anhydride **5**[9,12] by "one pot" methanolysis, thermal opening and esterification. Partial saponification of **6** by potassium hydroxide was

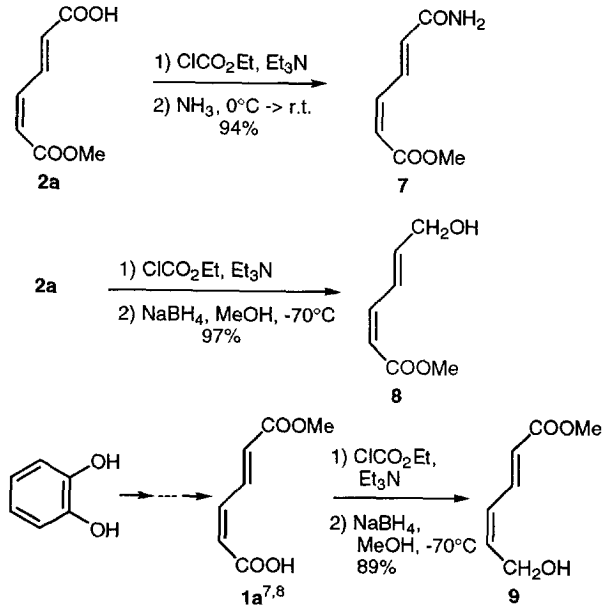


found to proceed with low selectivity and gave an **1a** + **2a** mixture in a 40:60 ratio, respectively, measured by integration of signals from 8.2 to 8.5 ppm of ^{1}H NMR spectrum. Fortunately the result was more interesting



by enzyme catalysed hydrolysis using *Pig Liver Esterase* (PLE) which led to a 4:96 ratio in 98% chemical yield. Compound **2a** was isolated in 88% yield after treatment of the **1a** + **2a** mixture by DMAP and formation of lactone **4a** (R = Me) from isomer **1a**.

Compound **2a** is a starting material for the preparation of other difunctionalized dienes. For instance compounds **7** and **8** were obtained by treatment of the intermediate anhydride by ammonia or sodium borohydride, respectively. Stereochemical assignments were staightforward upon analysis of ^{1}H NMR results for the alcohol-ester **8** and the isomeric product **9** obtained from **1a** (**8** : J_{H4H5} = 15.5 Hz,



J_{H2H3} = 11.3 Hz ; **9** : J_{H4H5} = 11.7 Hz, J_{H2H3} = 15.2 Hz (checked by several spin decoupling experiments)). On the other hand lactonisation of **1a** into **4a** also confirms these assignments.

Pig Liver Esterase and several other esterases have been mainly used in asymmetric synthesis.[13] However it also allowed, in some cases, the selective preparation of achiral compounds. For instance, in three recent reports, a moderate[14] or excellent[15] selectivity was pointed out. In this paper we show that the enzymatic hydrolysis of **6** is highly selective.

Experimental Section

NMR spectra were recorded on a Bruker AC 400 instrument (400 and 100 MHz for ^{1}H and ^{13}C, respectively). Samples were dissolved in deuteriochloroform with tetramethylsilane as the internal standard. Melting points were determined on a Reichert apparatus and are uncorrected. Elemental analyses were performed by the Service de Microanalyse, CNRS, ICSN, Gif-sur-Yvette. High resolution mass measurements were performed at the CRMPO (Rennes) with a Varian mat 311 spectrometer.

(2*Z*,4*E*)-Dimethyl-2,4-hexadienedioate (6) :

Anhydride **5** (2 g, 16 mmol), trimethyl orthoformate (20 mL) and MeOH (0.72 mL, 18 mmol) were stirred under reflux for 6 h. The reaction mixture was then evaporated. MeOH (20 mL) and 36M H_2SO_4 (2 mL) were

added and this solution was refluxed for 3 h. Evaporation, addition of CH_2Cl_2 (100 mL), washing (brine, 40 mL), extraction of the aqueous phase with CH_2Cl_2 (3 x 30 mL), drying of the combined organic phases ($MgSO_4$) then evaporation led to a solid. Recrystallization (ether/light petroleum, 1:2) yielded to 2.45 g (89%) of **6**. Mp 72-73°C. ^1H NMR : δ 3.82 (s, 6H, CH_3), 6.01 (d, 1H, *J* = 10.0 Hz, H-2), 6.17 (d, 1H, *J* = 15.0 Hz, H-5), 6.70 (dd, 1H, *J* = 10.0, 10.0 Hz, H-3), 8.46 (dd, 1H, *J* = 15.0, 10.0 Hz, H-4). ^{13}C NMR : δ 51.7, 51.9 ($\underline{C}H_3$) ; 124.3, 128.7, 138.7, 140.7 ($\underline{C}H$) ; 165.7, 166.5 ($\underline{C}O_2CH_3$). Anal. Calcd for $C_8H_{10}O_4$: C, 56.47 ; H, 5.92 ; O, 37.61. Found : C, 56.55 ; H, 5.67 ; O, 37.32.

(2*E*,4*Z*)-5-Methoxycarbonyl-2,4-pentadienoic acid (2a) :

Diester **6** (1 g, 5.88 mmol) was stirred with a buffer solution of KH_2PO_4 (0.1 M, pH 7, 25 mL) at 40°C then the pH was adjustated to 7.2 by addition of 1M NaOH. *Pig Liver Esterase* (350 units) was added and the pH was maintened at 7.2 with a pH stat. The reaction was allowed to proceed for 4 h until 5.88 mL (5.88 mmol) of 1M NaOH were added. The solution was then extracted with Et_2O (50 mL), the aqueous phase was acidified to pH 2 with 6M HCl and extracted with CH_2Cl_2 (4 x 30 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to leave 0.900 g (98%) of a mixture of **1a** and **2a** in the 4:96 ratio, respectively. A solution of this mixture (0.890 g, 5.7 mmol) and of 4-dimethylaminopyridine (0.070 g, 0.57 mmol) in toluene (9 mL) was stirred under reflux for 1 h. Cooling, addition of toluene (20 mL) and of 2M HCl (5 mL), stirring, extraction of the aqueous phase with toluene (2 x 10 mL), washing of the combined organic phases with saturated Na_2CO_3 (2 x 10 mL), drying ($MgSO_4$) and evaporation led to 0.095 g of 5-methoxycarbonylmethyl-2,5-dihydrofuran-2-one **4a** as an oil. ^1H NMR δ 2.66 (dd, 1H, *J* = 16.7, 6.9 Hz, one H of CH_2), 2.87 (dd, 1H, *J* = 16.7, 6.9 Hz, one H of CH_2), 3.75 (s, 3H, CH_3), 5.40 (m, 1H, *J* = 6.9, 2.0, 1.5 Hz, H-5), 6.18 (dd, 1H, *J* = 5.9, 2.0 Hz, H-3), 7.61 (dd, 1H, *J* = 5.9, 1.5 Hz, H-4) ; ^{13}C NMR δ 37.6 ($\underline{C}H_3$), 52.3 ($\underline{C}H_2$), 78.9 (C-5), 122.2 (C-3), 155.4 (C-4), 169.4 ($\underline{C}O_2CH_3$). The preceding combined aqueous phases were acidified by 2M HCl then extracted with CH_2Cl_2 (4 x 30 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to leave 0.787 g (88%) of **2a**. Mp 100-102°C. ^1H NMR : δ 3.80 (s, 3H, CH_3), 6.03 (d, 1H, *J* = 11.5 Hz, H-5), 6.13 (d, 1H, *J* = 15.5 Hz, H-2), 6.68 (dd, 1H, *J* = 11.5, 11.5 Hz, H-4), 8.49 (dd, 1H, *J* = 15.5, 11.5 Hz, H-3), 11.30 (br s, 1H, COOH). ^{13}C NMR :[16] δ 51.8 ($\underline{C}H_3$), 125.2 (C-5), 128.0 (C-2), 140.1 (C-4), 140.8 (C-3), 165.6 ($\underline{C}O_2CH_3$), 171.6 ($\underline{C}O_2H$). Anal. Calcd for $C_7H_8O_4$: C, 53.85 ; H, 5.16 ; O, 40.99. Found : C, 53.64 ; H, 4.92 ; O, 40.80.

(2*Z*,4*E*)-5-Methoxycarbonyl-2,4-pentadienoic acid (1a) :

Pyridine (110 mL), freshly prepared CuCl (10.8 g, 0.109 mol) and methanol (5.5 mL) were introduced under argon in a flask which could be connected with an hydrogenation apparatus at atmospheric pressure which was used with oxygen in this experiment. Argon was replaced by oxygen and the mixture was stirred at room temperature until 610 mL of oxygen were consumed. A mixture of catechol (2 g, 18 mmol), methanol (0.9 mL) and pyridine (37 mL) was then added dropwise for 1 h. The reaction was allowed to proceed until 407 mL more of oxygen were consumed. The reaction mixture was then evaporated and 3M HCl (200 mL) was added to the residue. Several extractions with CH_2Cl_2, drying ($MgSO_4$) and evaporation led to the crude (2Z,4Z)-5-methoxycarbonyl-2,4-pentadienoic acid as a brown solid. ^1H NMR δ 3.77 (s, 3H, CH_3); 6.01 (dd, 1H, *J* = 11.5, 0.9 Hz) and 6.03 (dd, 1H, *J* = 11.5, 0.9 Hz) (H-2 and H-5) ; 7.86 (ddd, 1H, *J* = 11.5, 11.5, 0.9 Hz) and 8.01 (ddd, 1H, *J* = 11.5, 11.5, 0.9 Hz) (H-3 and H-4) ; 11.35 (br s, 1H, COOH).

^{13}C NMR δ 51.7 (CH_3) ; 123.3, 124.7, 137.6, 140.1 (CH) ; 166.0 (CO_2CH_3) ; 171.0 (CO_2H). Water (450 mL) was added to the crude preceding product and the solution was heated at 90°C for 2.5 h then evaporated. The crude product was chromatographed on silica gel column (cyclohexane/ethyl acetate, 7:3) and 1.548 g (54.6% from cathecol) of **1a** was thus obtained. Mp 96-98°C (Litt.[7] 99-100). ^1H NMR : δ 3.80 (s, 3H, CH_3), 6.01 (d, 1H, *J* = 11.6 Hz, H-2), 6.16 (d, 1H, *J* = 15.5 Hz, H-5), 6.76 (dd, 1H, *J* = 11.6, 11.6 Hz, H-3), 8.38 (dd, 1H, *J* = 15.5, 11.6 Hz, H-4), 11.35 (br s, 1H, COOH). ^{13}C NMR :[16] δ 52.1 (CH_3), 123.8 (C-2), 129.5 (C-5), 138.4 (C-4), 142.7 (C-3), 166.5 (CO_2CH_3), 170.5 (CO_2H).

Methyl (2*Z*,4*E*)-5-carbamoyl-2,4-pentadienoate (7) :

Et_3N (2.9 mL, 20.5 mmol) then ethyl chloroformate (2 mL, 20.5 mmol) were added while stirring at 0°C to a solution of **2a** (3.03 g, 17.8 mmol) in THF (80 mL) under argon. The reaction mixture was stirred for 1h then a saturated solution of NH_3 in THF (100 mL) was added dropwise.The reaction was allowed to proceed for 30 min at 0°C then 1 h at room temperature. The reaction mixture was filtered under vacuum and the filtrate was evaporated to leave the crude product which was purified by addition of acetone (5 mL), filtration and evaporation of filtrate. The resulting oil gave **7** as white crystals when it was dissolved in the minimum amount of CH_2Cl_2 and crystallized by addition of Et_2O (yield : 2.6 g, 94%). Mp 111-115°C. ^1H NMR : δ 3.80 (s, 3H, CH_3), 5.90 (br s, 2H, NH_2), 5.96 (d, 1H, *J* = 11.4 Hz, H-2), 6.17 (d, 1H, *J* = 15.5 Hz, H-5), 6.65 (dd, 1H, *J* = 11.4, 11.4 Hz, H-3), 8.25 (dd, 1H, *J* = 15.5, 11.4 Hz, H-4). ^{13}C NMR : δ 51.7 (CH_3) ; 123.6, 131.5, 135.5, 141.0 (CH) ; 166.0, 167.6 (CO_2CH_3 and $CONH_2$). Anal. Calcd for $C_7H_9NO_3$: C, 54.19 ; H, 5.84 ; N, 9.03 ; O, 30.94. Found : C, 54.17 ; H, 5.74 ; N, 8.92 ; O, 31.02.

Methyl (2*Z*,4*E*)-6-hydroxy-2,4-hexadienoate (8) and methyl (2*E*,4*Z*)-6-hydroxy-2,4-hexadienoate (9)

Et_3N (187 µL, 1.32 mmol) was added at 0°C under argon to a stirred solution of **2a** or **1a** (0.200 g, 1.28 mmol) in dry THF (3 mL), then ethyl chloroformate (128 µL, 1.32 mmol) was introduced dropwise at the same temperature. The reaction was allowed to proceed for 1 h then the reaction mixture was filtered and the precipitate was washed with THF (4 x 1 mL). Filtrate was cooled to -70°C. $NaBH_4$ (0.122 g, 3.22 mmol) was introduced in several times then methanol (650 µL) was added dropwise under stirring. The reaction was allowed to proceed at the same temperature for 1 h then 1M HCl (8 mL) was added slowly while the mixture was allowed to warm up slowly to room temperature. Evaporation of THF, extraction with CH_2Cl_2 (5 x 5 mL), neutralization of the combined organic phases (saturated Na_2CO_3 then brine), drying ($MgSO_4$) and evaporation led to the crude product. Purification by column chromatography on silica gel (CH_2Cl_2/Et_2O, 9:1) led either to 0.156 g (97%) of **8** or to 0.144 g (89%) of **9** as colorless oils. **8** : ^1H NMR δ 2.33 (br s, 1H, OH), 3.73 (s, 3H, CH_3), 4.30 (dd, 2H, *J* = 5.3, 1.4 Hz, CH_2), 5.69 (d, 1H, *J* = 11.3 Hz, H-2), 6.18 (dt, 1H, *J* = 15.5, 5.3 Hz, H-5), 6.61 (dd, 1H, *J* = 11.3, 11.3 Hz, H-3), 7.52 (ddt, 1H, *J* = 15.5, 11.3, 1.4 Hz, H-4) ; ^{13}C NMR :[16] δ 51.3 (CH_3), 62.7 (CH_2), 117.4 (C-2), 126.4 (C-4), 142.2 (C-5), 144.1 (C-3), 166.8 (CO_2CH_3). HRMS : Calcd for $C_7H_{10}O_3$: 142.06299. Found : 142.0629 ; **9** : ^1H NMR δ 2.35 (br s, 1H, OH), 3.75 (s, 3H, CH_3), 4.43 (dd, 2H, *J* = 6.6, 1.4 Hz, CH_2), 5.92 (d, 1H, *J* = 15.2 Hz, H-2), 5.99 (dtd, 1H, *J* = 11.7, 6.6, 1.0 Hz, H-5), 6.19 (ddt, 1H, *J* = 11.7, 11.7, 1.4 Hz, H-4), 7.57 (ddt, 1H, *J* = 15.2, 11.7, 1.0 Hz, H-3) ; ^{13}C NMR :[16] δ 51.7 (CH_3), 58.8 (CH_2), 122.6 (C-2), 127.5 (C-4), 138.5 (C-5), 138.8 (C-3), 167.5 (CO_2CH_3). HRMS : calcd for $C_7H_{10}O_3$: 142.06299. Found : 142.0629.

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