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Expeditious Synthesis of the Four Isomers of Methyl Dimorphecolate

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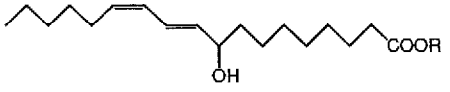
Abstract : *The four geometric isomers of methyl dimorphecolate 3 were synthezised by direct, palladium catalyzed, coupling of the two olefinic parts of the conjugated diene system.*

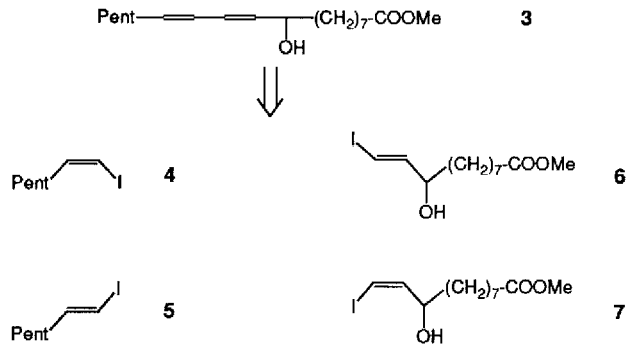
Dimorphecolic acid **1** as well as its congener coriolic acid **2** (or their esters), commonly found in vegetable oils, are natural metabolites of linoleic acid. They have received considerable interest since the discovery of their possible role as self defensive substances against diseases[1,2]. In the case of tomato plant *Lycopersicum esculentum*, for instance, protection was reported[2] not only to involve methyl dimorphecolate **3** but also geometric isomers. In order to assure their identification and comparative biological studies, synthetic materials of the four stereoisomers were required. Moreover, it was important to be able to characterise and locate by specific gas phase ion-molecule reactions/mass spectrometry the hydroxy diene system[3]. Until now, by contrast with the coriolic acid series, the synthesis of dimorphecolic acid has been achieved through a limited number of pathways with no report on any of its stereoisomers[4].



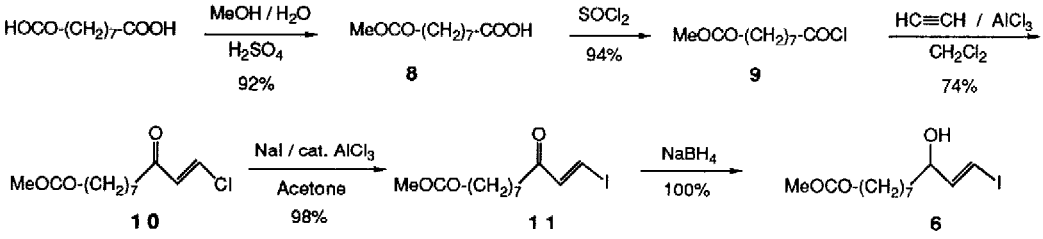
1 R = H Dimorphecolic acid
3 R = Me Methyl dimorphecolate

2 Coriolic acid

In this context, an attractive synthetic strategy was the coupling of two olefinic parts having already the requisite stereochemistry. Provided that the coupling stage occured with complete stereocontrol, such a strategy avoids tedious purifications on the final molecule. Cost and ready availability of starting materials should also be considered since these compounds should be synthesized on semi-preparative scale. We have succesfully used this approach for the synthesis of dienic insect sex pheromones[5], using the carbocupration reaction[6] for the Z moiety, the hydroalumination reaction[7] for the E one, and a palladium catalyzed reaction[8] for the final coupling.

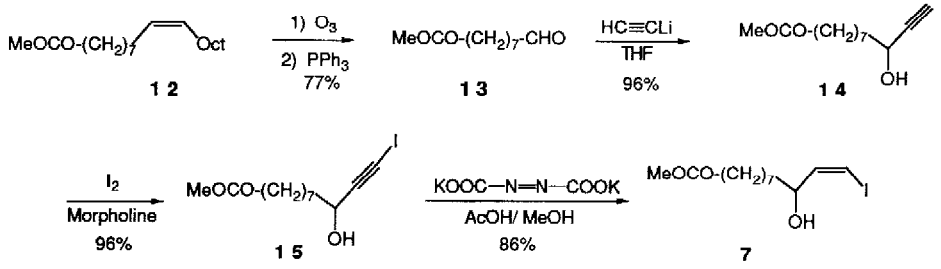


In the case of methyl dimorphecolate, **3**, we needed to prepare the alkenyl iodides **4-7**. The Z iodide **4** is easily available through reaction of di-pentyl cuprate with acetylene, followed by iodination[6], in 74% yield and >99% isomeric purity[9]. Its E counterpart **5** was prepared by hydroalumination of 1-heptyne with diisobutyl aluminium hydride, followed by iodination[7], in 76% yield and >99% purity[9]. The iodides **6** and **7** could not be prepared by the same way. The syntheric sequence leading to **6** is the following :



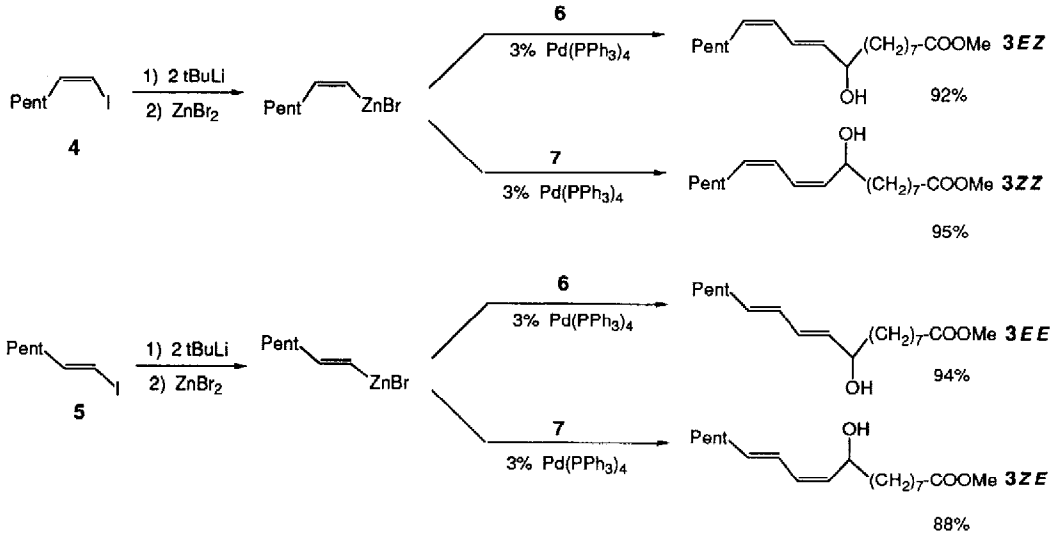
Azelaic monomethyl ester **8** (also commercially available) was readily prepared from the diacid , according to ref.10 in 92% yield. The corresponding acid chloride **9**, prepared in 94% yield with $SOCl_2$[11], reacted with acetylene, in the presence of aluminium chloride[12] to give the E β-chlorovinyl ketone **10** (E/Z : 90/10, yield : 74%). Transhalogenation[13] gave, in 98% yield the pure E (> 99%)[14] alkenyl iodide **11**, which was selectively reduced[15] to the required alcohol **6** in quantitative yield (E purity : 99.1%[9]). The overall yield of this sequence is 62.7%, based on the starting diacid.

On the other hand the Z alkenyl iodide **7** was prepared from methyl oleate **12** in 61% overall yield and 99.9% isomeric purity[9], according to the following scheme :



Ozonolysis of technical grade methyl oleate **12**, followed by the reduction of the ozonide with triphenylphosphine (more efficient than Me_2S) gave, in 77% yield, the required aldehyde-ester **13**. Monolithio-acetylene[16] reacted selectively with the aldehyde function to afford the propargylic alcohol **14**, in 96% yield. This alcohol was transformed into the iodo-alkyne **15** with the iodine / morpholine complex[17], which in turn was submitted to diimide reduction[18] without protection of the hydroxy functionality[19], in 86% yield[20].

Having in hand all the necessary iodides, the final coupling was performed on the free alcohol, to avoid a deprotection on the final compound, a step which may slighly isomerise the very fragile dienic system. The non-functionalized alkenyl iodides **4** or **5** were transformed into the nucleophilic species, by : 1) metal-halogen exchange in Et_2O with 2 eq. of t-BuLi and 2) transmetallation into the zinc derivative by addition of 1 eq. of $ZnBr_2$ in THF. 2.5 eq. of the reagent were used (one eq. just serves to deprotonate the free hydroxy group of **6** or **7**) in the coupling step with 3% $Pd(PPh_3)_4$ as the catalyst. The coupling reaction is quantitative and very fast, occuring in less than 1h at 5°-10°C. As expected, the alkenyl zinc reagent does not react at all with the ester functionality and the free hydroxy group has no deleterious effect.



A simple flash chromatography allows the obtention of the pure isomers[21] of methyl dimorphecolate **3** in the high yields stated in the above scheme. The purity of each stereoisomer was checked by capillary column gas chromatography[9] where all four isomers were perfectly separable : **3EZ** >99.9% ; **3ZZ** 99% (1% of EZ isomer) ; **3EE** >99.9% ; **3ZE** 99% (1% of EE isomer). In this way enough material was synthesized for the mass spectroscopic studies[3] and for the biological tests. The biological results will be reported in due time. The methodology outlined above may be used for the synthesis of optically active material since methods for obtaining chiral iodo-alkenols such as **6** and **7** are known[22,23]. It should also pointed out that other biologically active dienols, such as coriolic acid **2** could be available through the same way.

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20. A few percent of fully reduced material were easily separated by flash column chromatography.
21. All the analytical data are in agreement with the proposed structures. NMR data ($CDCl_3$) on a Varian Gemini 300 instrument : **3EZ** : ^1H (ppm): 6.50 (dd, 1H, J = 11.0 and 15.1 Hz); 5.95 (dd, 1H, J = 11.0 and 10.7 Hz); 5.65 (dd, 1H, J = 15.1 and 7.0 Hz); 5.45 (dt, 1H, J = 10.7 and 6.3 Hz); 4.15 (dt, 1H, J = 7.0 and 7.0 Hz). ^{13}C (ppm) : 174.0 (COO), 136.1 (C10), 132.8 (C13), 128.0 (C12), 125.8 (C11), 72.8 (CHOH). **3ZZ** : ^1H (ppm): 5.80 (m, 2H, J = 10.8 Hz); 5.40 (m, 2H, J = 10.8 Hz); 4.43 (dt, 1H, J = 6.3 Hz). ^{13}C (ppm) : 173.9 (COO), 135.1 (C10), 134.5 (C13), 125.5 (C12), 123.9 (C11), 68.1 (CHOH). **3EE** : ^1H (ppm): 6.10 (m, 2H, J = 10.2, 14.4 and 14.6 Hz); 5.60 (m, 2H, J = 6.7, 6.9, 14.4 and 14.6 Hz); 4.10 (dt, 1H, J = 6.9 Hz). ^{13}C (ppm) : 174.0 (COO), 135.5 (C10), 133.9 (C13), 131.0 (C12), 129.2 (C11), 72.9 (CHOH). **3ZE** : ^1H (ppm): 6.54 (dd, 1H, J = 10.9 and 10.9 Hz); 6.42 (dd, 1H, J = 10.9 and 15.2 Hz); 5.62 (dd, 1H, J = 10.9 and 7.4 Hz); 5.44 (dt, 1H, J = 15.2 and 7.1 Hz); 4.45 (dt, 1H, J = 6.9 and 7.0 Hz). ^{13}C (ppm) : 173.4 (COO), 135.9 (C10), 132.4 (C13), 124.9 (C12), 122.8 (C11), 72.8 (CHOH). NH_3-CIMS (Nermag R-10-10C instrument) : ions at m/z 328, 310 and 293 corresponding respectively (*cf* ND_3-CIMS) to $[M+NH_4]^+$, $[M+NH_4-H_2O]^+$ and $[M+NH_4-H_2O-NH_3]^+$ for the four isomers.
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