Catalytic Hydrogenation/Enzymic Hydrolysis as a Route from Alkyl Alka-2,4-dienoates to (*Z*)-Alk-3-enoic Acids

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(*Z*)-Alk-3-enoic acids of no less than 94% geometrical purity have been obtained from the respective alkyl alka-2,4-dienoates after hydrogenation over chromium hexacarbonyl followed by hydrolysis of the resulting products using porcine pancreatic lipase or KOH in H_2O/MeOH.

(*Z*)-Alk-3-enoic acids, some of which are the pheromones of certain coleopterous insects or intermediates used in their synthesis,[1–3] are most often obtained either by the partial reduction of the triple bond in alk-3-ynoic acids (see, *e.g.*, refs. 3–5) or by Wittig *cis*-olefination of alkanals (see, *e.g.*, refs. 6–7). We have studied the feasibility of preparing (*Z*)-alk-3-enoic acids from the derivatives of respective alka-2,4-dienoic acids using hydrogenation over chromium hexacarbonyl as the key step.

The 1,4-addition of H_2 to the complexes formed on interaction of conjugated dienes with $Cr(CO)_6$ occurs with high *cis* stereoselectivity,[8,9] and in recent years has successfully been applied to the synthesis of fragrance substances.[10,11] However, only one case of the desired transformation has been reported, namely, the reduction of alkyl sorbates, such as **1a**, to the respective (*Z*)-hex-3-enoates of type **2a** (refs.10 and 11).

We have found that the above procedure can be successfully extended to the higher dienoates **1b–d** (Table 1). Just as in the case of methyl sorbate (**1a**), the 1,4-hydrogenation of **1b** and **1c** affords, in addition to the target methyl (*Z*)-alk-3-enoates **2a–c**, minor quantities of their 3(*E*)- and 2(*E*)-isomers (**3a–c** and **4a–c**, respectively). Hydrogenation of the dienoate **1d**, the molecule of which contains a methyl group at C(3), proceeds with practically 100% selectivity (Scheme 1).

It is to be noted that the starting dienoates **1b–d**, prepared by Horner–Emmons olefination of aldehydes R^2CHO with allylic phosphonates $(EtO)_2P(O)CH_2C(R^1)=CHCO_2R$, contained the 2(*E*), 4(*E*)- and 2(*Z*), 4(*E*)-isomers in the ratios 90:10 (for **1b,c**) or 65:35 (**1d**). However, in each case both of these stereoisomers on hydrogenation over $Cr(CO)_6$ gave the respective (*Z*)-alk-3-enoates as the main reaction product.

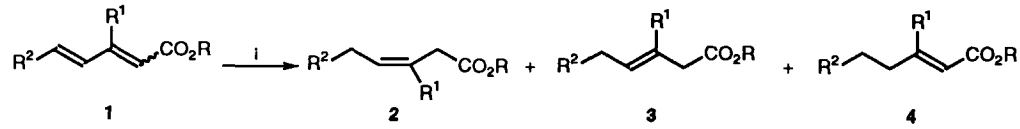
Table 1 The products of hydrogenation of alka-2,4-dienoic acid derivatives over chromium hexacarbonyl.

Substrate (final product)	Solvent	Yield[a,b] (%)	Isomer composition[b,c] (%)			B.p. /°C (Torr)
			2	3	4	
1a	Hexane	59	87	2	11	75(20)
(**2e**)		(75)[d]	(84)[d]	(2)[d]	(14)[d]	
		(80)[e]	(95)[e]	(2)[e]	(3)[e]	
1b	Hexane	70	96	1	3	106(10)
(**2g**)		(78)[d]	(93)[d]	(1)[d]	(6)[d]	
		(50)[e]	(99)[e]	(1)[e]	(0)[e]	
1c	Benzene	60	96	2	2	140 (3)
(**2h**)		(72)[d]	(94)[d]	(2)[d]	(4)[d]	
1d	Benzene	62	100	0	0	90 (2)
(**2i**)		(74)[d]	(95)[d]	(0)[d]	(5)[d]	
1e(**2e**)	Benzene	40[f]	12	11	77	125–130(40)
1f(**2e**[g])	H_2O	70[g]	36[g]	8[g]	56[g]	125–130(40)[g]

[a]Yield of the isolated mixture of isomers. [b]Data pertaining to the mixture of isomeric acids obtained after hydrolysis of the hydrogenation products are given in parentheses. [c]Determined from GLC analyses and/or ^1H NMR spectra. [d]Alkaline hydrolysis. [e]Enzymic hydrolysis, at 50–80% conversion. [f]With extensive resinification. [g]For the mixture of acids **2e**, **3e** and **4e** upon acidification of the crude hydrogenation product.

Mild alkaline hydrolysis of esters **2a–d** liberated the corresponding target acids **2e, g–i**. Unfortunately, the hydrolysis was accompanied by partial isomerisation, mainly to the 2(*E*)-counterparts (**4e,g–i**), to the extent of *ca.* 5%.

In order to avoid this isomerisation, which was obviously due



2a–d —(ii or iii)→ 2e,g–i

(R = alkyl) (R = H)

1–4	R	R^1	R^2	2–4	R	R^1	R^2
a	Me	H	Me	g	H	H	Am
b	Me	H	Am	h	H	H	$MeCH(OH)(CH_2)_5$
c	Me	H	$MeCH(OH)(CH_2)_5$	i	H	Me	Am
d	Pr^i	Me	Am				
e	H	H	Me				
f	K	H	Me				

Scheme 1 *Reagents and conditions*: i, H_2 (50 atm)/$Cr(CO)_6$ (*ca.* 10 mol.%), 160–180 °C, 2–4 h, for solvents, see Table 1; ii, KOH (3 equiv.)/H_2O–MeOH (1:3, v/v), r.t., then HCl to pH 2; iii, PPL (25% w/w)/0.05 M phosphate buffer (pH 7.0)–Et_2O (1:5, v/v), r.t., with gradual addition of 1 M aqueous NaOH to maintain the pH at 7.0.

to the effect of the alkaline medium, we made use of an early observation[12] that porcine pancreatic lipase (PPL) hydrolyses the esters of (*E*)-alk-2-enoic acids much slower than their unconjugated isomers. In fact, the PPL-catalysed hydrolysis of esters **2a** and **2b** at pH 7.0 afforded samples of acids **2e** and **2g** of higher geometrical purity with respect to the starting esters (Table 1) whereas admixtures of the 2(*E*)-isomers accumulated in unconverted material. Interestingly, the enzymic hydrolysis in the biphasic system phosphate buffer–Et_2O proceeds much slower for **2b** than for **2a**; this may be due to their different lipophilicity.

We have also tried to obtain the (*Z*)-alk-3-enoic acids by circumventing the hydrolysis step. To this end, the hydrogenation of the free sorbic acid (**1e**) and its potassium salt (**1f**) was studied. To our surprise, the hydrogenation of **1e** and **1f** proceeded with low selectivity (Table 1); in the former case it was accompanied by extensive resinification. Attempts to hydrogenate the derivatives of **1e**, in which the carboxyl group was protected by groups easily removable under neutral or mild acidic conditions ($R = SiMe_3$, CH_2OMe, CH_2CCl_3), were equally unsuccessful.

The preparative value of the two-step synthetic sequence developed depends on the accessibility of the starting dienoates and is illustrated by the transformation of **1b** to (*Z*)-dec-3-enoic acid **2g**, the aggregation pheromone of the furniture carpet beetle *Anthrenus flavipes* (*Dermestidae*),[1] and the formal synthesis of (±)-ferrulactone II, the pheromone of the rusty grain beetle *Cryptolestes ferrugineus* (*Cucujidae*), for which the hydroxy acid **2h** is the nearest precursor (see refs. 2–7). Our results also allow for the prospect of employing the lipase-catalysed hydrolysis for a clean separation of alkyl (*E*)-alk-2-enoates from their non-conjugated isomers in otherwise inseparable mixtures.

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