A Facile Synthesis of 3,7-Unsaturated Esters via Two Consecutive Claisen-Cope Rearrangements

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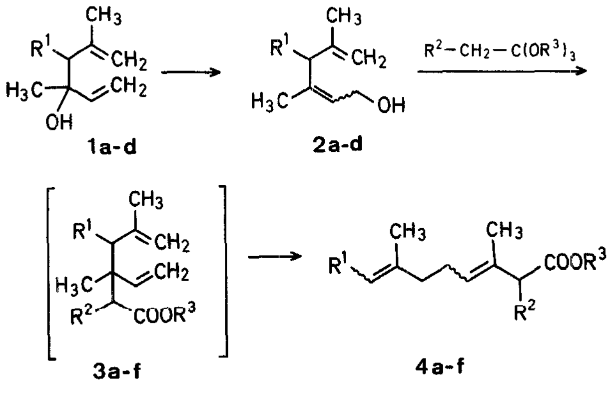
As part of our continuing investigations to utilize mesityl oxide as a 6 carbon atom chain extender[1], we were interested in the transformation of the dienols **1** into other functionalized 1,5-hexadiene systems. Recently, Büchi and co-workers have reported the transformation of the hydroxy group of **1** into a formyl group attached to the 1,5-hexadiene system[2]. Such systems activated by a carbonyl group are also obtainable in the initial step of two consecutive Claisen-Cope rearrangements[3], and need relatively low temperatures for thermal reorganization. On the other hand, it is well known that highly substituted 1,5-hexadiene systems with alkyl groups in the 3 and/or 4 positions also rearrange relatively easily[4]. In this communication we wish to report a novel combination of the Claisen and Cope rearrangements to yield alka-3,7-dienoates **4a–f** via 1,5-hexadiene systems of type **3**, bearing a non-conjugated ester group, generated by the reaction of **2** and ortho esters[5].

Dienols **1b–d** were prepared as described previously[1] by the condensation of the corresponding halides with mesityl oxide followed by reaction with vinylmagnesium bromide. Bromination of **1** with 0.4 equiv of phosphorus tribromide (in ether, 0° for 3 h), acetoxylation with 2.5 equiv (vs. bromide) of sodium acetate (in dimethylformamide, 30° for 12 h), and saponification with 10% aqueous potassium hydroxide/methanol (2 equiv vs. acetate, 40° for 3 h) afforded **2** in ~75% overall yield.



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Claisen rearrangement of **2** with 5 equiv of ortho ester in the presence of 2,6-dimethylphenol catalyst (7 mol % vs. **2**) at 145–155° for 3–5 h yielded **3** together with a small amount of **4** (Table 1). The use of aliphatic acid catalyst (e.g. 2-methylpropanoic acid) was not advantageous owing to the esterification of **2**. Cope rearrangement of **3** at elevated temperatures, 180–200°, the reaction being carried out *in situ* if desired, gave **4** in good yields (Table 2). Thermal rearrangements of the isopropenyl group to give fused benzene or furan rings could not be observed in **3c, d**. Analyses by G.L.C. indicated that the products **4b–d** contained mixtures of (3*Z*,7*Z*)/(3*E*,7*Z*) and (3*Z*,7*E*)/(3*E*,7*E*) [~7:68:25] and the total *E*/*Z* ratio of positions 3 and 7 was approximately 3:7 and 8:2, respectively. In the case of **4a, e, f**, the *E*/*Z* ratio of the 3 position varied widely with the substituent of the ortho esters in the range 55:45 to 86:14.

3,5-Dimethyl-2,5-hexadien-1-ol (2a):

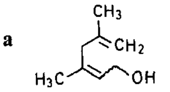
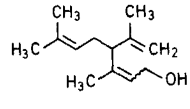
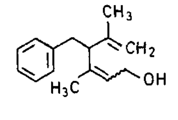
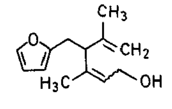
To a solution of 3,5-dimethyl-1,5-hexadien-3-ol[6] (**1a**; 37.8 g, 0.3 mol) and pyridine (0.5 ml) in ether (200 ml) is added phosphorus tribromide (32.4 g, 0.12 mol) in ether (60 ml) at 0–3°. Stirring is continued for 3 h. The mixture is poured into water (300 ml), extracted with ether (600 ml), and the extracts concentrated to yield the crude bromide (53.6 g) which is then acetoxylated with sodium acetate (58.1 g, 0.71 mol) in dimethylformamide (800 ml) at 30° for 12 h to give the acetate; yield: 41.9 g (83 %); b.p. 95–99°/23 torr.

Saponification of the acetate (41.9 g) with potassium hydroxide (28 g) in water (250 ml) and methanol (900 ml) at 40° for 3 h followed by evaporation of methanol and extraction with ether gives **2a**; yield: 28.8 g (92 % based on acetate, 76 % overall); b.p. 89–93°/20 torr.

$C_8H_{14}O$	calc.	C 76.14	H 11.18
(126.2)	found	76.02	11.32

I.R. (neat): ν_{max} = 3320, 1640, 1000, 889 cm^{-1}.

Table 1. Claisen Rearrangement of Compounds **2** to give Products **3**+**4**

Substrate No.	Structure	b.p./torr of **2**	Ortho ester	Reaction conditions temp./time	Yield [%] of **3**+**4**	Ratio of **3**:**4**	Product **3**	b.p./torr of **3**	Molecular formula[a]
2a		89–93°/20	$H_3C—C(OC_2H_5)_3$	150–155°/3 h	83	95:5	**3a**	62–65°/0.3	$C_{12}H_{20}O_2$ (196.3)
2b		90–91°/0.4	$H_3C—C(OC_2H_5)_3$	150–153°/4.5 h	78	93:7	**3b**	103–106°/0.3	$C_{17}H_{28}O_2$ (264.4)
2c		115–118°/0.5	$H_3C—C(OC_2H_5)_3$	150–154°/4 h	76	70:30	**3c**	—[b]	—[b]
2d		100–103°/0.3	$H_3C—C(OC_2H_5)_3$	147–152°/4 h	71	70:30	**3d**	—[b]	—[b]
2a	as above	—	$C_2H_5—C(OC_2H_5)_3$	145–150°/3 h	77	95:5	**3e**	124–128°/25	$C_{13}H_{22}O_2$ (210.3)
2a	as above	—	$C_6H_5CH_2—C(OCH_3)_3$	145–150°/3 h	75	95:5	**3f**	114–117°/0.35	$C_{17}H_{22}O_2$ (258.4)

[a] Products **3a, b, e, f** gave satisfactory microanalyses (C, H, ±0.30).

[b] Separation of mixture by fractional distillation was not possible.

Table 2. Cope Rearrangement of Products **3** to give **4**

Substrate **3**	Reaction conditions temp./time	Yield [%] of **4**	b.p./torr	Molecular formula[a]	Stereochemistry of **4**[b]
3a	193–195°/5.5 h	92	115–119°/2	$C_{12}H_{20}O_2$ (196.3)	3-(*E*/*Z*)=55:45
3b	190–193°/4 h	91	114–117°/0.5	$C_{17}H_{28}O_2$ (264.4)	(3*Z*,7*Z*)=7; (3*E*,7*Z*) + (3*Z*,7*E*)=68; (3*E*,7*E*)=25
3c[c]	180–185°/4 h	90	134–137°/0.15	$C_{19}H_{26}O_2$ (286.4)	(3*Z*,7*Z*)=7; (3*E*,7*Z*) + (3*Z*,7*E*)=71; (3*E*,7*E*)=22
3d[c]	180–185°/4 h	82	114–117°/0.15	$C_{17}H_{24}O_3$ (276.4)	(3*Z*,7*Z*)=9; (3*E*,7*Z*) + (3*Z*,7*E*)=64; (3*E*,7*E*)=27
3e	197–200°/5 h	90	78–81°/1.5	$C_{13}H_{22}O_2$ (210.3)	3-(*E*/*Z*)=71:29
3f	190–195°/5 h	90	116–118°/0.25	$C_{17}H_{22}O_2$ (258.4)	3-(*E*/*Z*)=86:14

[a] Products gave satisfactory microanalyses (C ±0.28, H ±0.26). N.M.R., I.R. and Mass spectral data are in agreement with the structure.

[b] Determined by G.L.C. analyses; **4a, e, f:** Silicone DC QF-1 (3 m) 10 % on Chromosorb W (AW); **4b:** Silicone DC-550 (2 m) 10 % on Chromosorb W (AW); **4c, d:** PEG 20M (2 m) 10 % on Chromosorb W (AW).

[c] Mixture of **3** and **4** described in Table 1 was used.

^{1}H-N.M.R. (CCl$_4$): $\delta = 1.49$, 1.56 (s, 3H, CH$_3$); 2.57 (*E*) and 2.63 (*Z*) (s, 2H, CH$_2$, $E/Z = 75/25$); 3.93 (d, 2H, CH$_2$, $J = 7$ Hz); 4.24 (s, 1H, OH); ~4.57–4.62 (m, 2H, =CH$_2$); 5.26 ppm (t, 1H, =CH, $J = 7$ Hz).

Ethyl 3,5-Dimethyl-3-vinyl-5-hexenoate (3a):

A mixture of **2a** (25.2 g, 0.2 mol), ethyl orthoacetate (162 g, 1 mol), and 2,6-dimethylphenol (1.7 g, 14 mmol) is heated in a flask equipped with a Claisen adapter at 150–155° for 3 h until ethanol no longer distills from the system. After cooling, ethyl orthoacetate is removed under reduced pressure (20 torr) and distillation of the residue gives crude **3a** (34.2 g) which is purified by silica gel column chromatography (eluent: benzene) to yield a mixture (**3a**/**4a** = 95/5); yield: 32.6 g (83%); subsequent fractional distillation gives pure **3a**; yield: 26.3 g (67%); b.p. 62–65°/0.3 torr.

C$_{12}$H$_{20}$O$_2$	calc.	C 73.42	H 10.27
(196.3)	found	73.28	10.49

I.R. (neat): $\nu_{\max} = 1736$, 1640, 1120, 1040, 896 cm^{-1}.

^{1}H-N.M.R. (CCl$_4$): $\delta = 1.04$ (s, 3H, CH$_3$); 1.12 (t, 3H, CH$_3$, $J = 7$ Hz); 1.62 (s, 3H, CH$_3$); 2.10 (s, 2H, CH$_2$); 2.16 (s, 2H, CH$_2$); 3.94 (q, 2H, CH$_2$, $J = 7$ Hz); 4.57, 4.71 (s, 2H, =CH$_2$); 4.81 (d, 1H, =CH, $J = 18$ Hz); 4.83 (d, 1H, =CH, $J = 10$ Hz); 5.80 ppm (dd, 1H, =CH, $J = 10$ and 18 Hz).

Ethyl 3,7-Dimethyl-3,7-octadienoate (4a):

A sample of **3a** (19.6 g, 0.1 mol) is heated at 193–195° for 5.5 h under a nitrogen atmosphere. Analysis by G.L.C. [silicone DC QF-1, 3 m, 160°] shows that the *E*/*Z* ratio of **4a** is 55:45 with 98% conversion of **3a** and >97% selectivity of **4a**. After cooling, distillation gives pure **4a**; yield: 18.0 g (92%); b.p. 115–119°/2 torr.

C$_{12}$H$_{20}$O$_2$	calc.	C 73.42	H 10.27
(196.3)	found	73.31	10.44

I.R. (neat): $\nu_{\max} = 1735$, 1668, 1645, 1038, 989 cm^{-1}.

^{1}H-N.M.R. (CCl$_4$): $\delta = 1.14$ (t, 3H, CH$_3$, $J = 7$ Hz); 1.60 (s, 6H, CH$_3$); ~1.98 (m, 4H, CH$_2$CH$_2$); 2.77 (*E*) and 2.84 (*Z*) (s, 2H, CH$_2$, $E/Z = 55/45$); 3.96 (q, 2H, CH$_2$, $J = 7$ Hz); 4.55 (s, 2H, =CH$_2$); ~5.10 ppm (m, 1H, =CH).

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