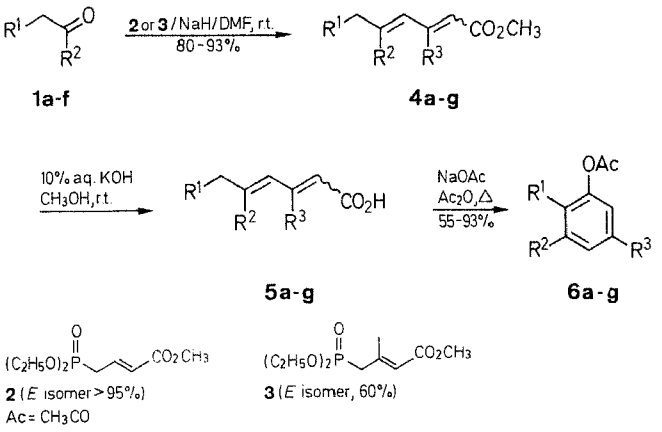

1	R^1	R^2	4–6	R^1	R^2	R^3
a	H	H	**a**	H	H	H
b	CH_3	H	**b**	CH_3	H	H
c	H	CH_3	**c**	H	CH_3	H
d	$-(CH_2)_4-$		**d**	H	CH_3	CH_3
e	i-C_3H_7	H	**e**	$-(CH_2)_4-$		CH_3
f	C_8H_{15}	H	**f**	i-C_3H_7	H	CH_3
			g	C_8H_{15}	H	CH_3

C_8H_{15} = (*R*)-2-(6-methyl-5-heptenyl); structure **1f** represents (*R*)-citronellal

Benzocyclization of 2,4-Hexadienoic Acids. Synthesis of (*R*)-(−)-Curcuphenol Acetate[1]

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A simple and general benzocyclization sequence, useful in the conversion of α-methylene ketones/aldehydes **1a–f** to phenolic acetates **6a–g** via the dienoic acids **5a–g** is presented. The technique has provided a new route to the terpenoids, thymol acetate **(6f)** and (*R*)-(−)-curcuphenol acetate **(6g)**.

The formation of a new benzene ring in the reaction of certain aryl unsaturated acids with acetic anhydride under reflux with or without anhydrous sodium acetate[2,3] prompted us to study under similar conditions the benzocyclization propensity of a few 2,4-dienoic acids. The 2,4-dienoic acids **5a–g** were prepared from the carbonyl compounds **1a–f** by Horner[4] reaction with either diethyl 3-methoxycarbonyl-2-propenylphosphonate[5] **(2)** or diethyl 3-methoxycarbonyl-2-methyl-2-propenylphosphonate[6] **(3)**, followed by mild basic hydrolysis of the resulting *E*/*Z*-Stereoisomeric dienoates **4a–g** (Table 1).

The dienoic acids **5a–g**, without purification or separation of isomers, were directly subjected to cyclization by heating to reflux under stirring with fused sodium acetate and acetic anhydride.[2] The crude product obtained on cyclization proved to be a mixture of the phenolic acetate **6a–g** and the mixed anhydride of the dienoic acid **5a–g** and acetic acid as revealed by IR and ^{1}H-NMR data. On column chromatography of the mixture over silica gel the anhydrides got cleaved to the constituent acids. The phenolic acetates **6a–g** were readily separated on the column from the more polar dienoic acids. The acetates **6a–f** were identified by comparison with the authentic acetates prepared from the corresponding phenols, namely, phenol, *o*-cresol, *m*-cresol, 3,5-dimethylphenol, 7-methyl-5-tetralol and thymol respectively. (*R*)-(−)-Curcuphenol acetate **(6g)** was characterized from rotational and spectral data[13,14] reported in literature.

Benzocyclization of 2,4-dienoic acids provides a convenient route to terpenoids, as has been exemplified in the present synthesis of thymol acetate **(6f)** and (*R*)-(−)-curcuphenol acetate **(6g)**, the latter occurring in *Garuleum sonchifolium*[13] in the (*R*)- and in *Mutisia homoeantha*[15] in the (*S*)-configuration. Approaches different from the one now under communication have been employed in the earlier syntheses of (±)-[16] (−)-[14] curcuphenol and its (±)-methyl ether.[17]

Methyl 3-methyl-6-(6-methyl-5-hepten-2-yl)-2,4-hexadienoate (4g); Typical Procedure:

To a stirred slurry of sodium hydride (1.08 g, 45 mmol) in dry dimethylformamide (50 ml) at room temperature is added a solution of **3** (11 g, 44 mmol) in dry dimethylformamide (25 ml), in such a way that the reaction is under control. The mixture is stirred for a further period of 1 h. (*R*)-(+)-Citronellal (**1f**; $[\alpha]_D^{30}$ + 12°, neat; 6.2 g, 40 mmol) is slowly added to the above cooled reaction mixture under stirring. After stirring overnight, the mixture is diluted with water (250 ml) and extracted with ether (5 × 50 ml), after saturating the aqueous phase with sodium chloride. The combined ether extract is washed with water (2 × 100 ml) and dried with sodium sulfate. Removal of solvent and other volatiles under reduced pressure gives practically pure **4g**; yield: 7.8 g (82%) (Table 1).

Table 1. 2,4-Dienoates **4a–g** Prepared

Reactants	Product	Yield (%)	b.p. (°C)/torr	Lit. b.p. (°C)/torr	IR[a] (Film) ν (cm^{-1})	^{1}H-NMR[b] (CCl_4/TMS) δ (ppm)	Geometry of Double Bond (% *E*) (from ^{1}H-NMR)	
							C_2–C_3	C_4–C_5
1a + 2	**4a**	93	84/25	75/15[7]	1720, 1640, 1610	5.56 (d, J = 15 Hz, 1H); 6.0–6.25 (m, 2H); 7.5 (dd, $J_{2,3}$ = 15 Hz, $J_{3,4}$ = 10 Hz, 1H)	100	100
1b + 2	**4b**	90	110/25	99–100/21[8]	1725, 1635, 1610	5.54 (d, J = 15 Hz, 1H); 6.0–6.25 (m, 2H); 7.1 (dd, $J_{2,3}$ = 15 Hz, $J_{3,4}$ = 10 Hz 1H)	100	100
1c + 2	**4c**	85	108/25	90/13[9]	1710, 1635, 1610	5.65 (d, J = 15 Hz, 1H); 5.90 (d, J = 10 Hz, 1H); 7.45 (dd, $J_{2,3}$ = 15 Hz, $J_{3,4}$ = 10 Hz, 1H)[c]	100	–
1c + 3	**4d**	87	96/25	–[10]	1720,1625	5.57 (br s); 5.65 (br s); 6.5 (br s)	90	–
1d + 3	**4e**	80	130/3	–[d]	1720, 1625	5.52 (br s); 5.6 (br s); 6.17 (br s)	90	–
1e + 3	**4f**	88	130/10	–[11]	1720, 1635, 1610	5.5 (br s); 5.6 (br s); 5.8–6.23 (m); 7.6 (d, J = 16 Hz)	67	100
1f + 3	**4g**	82	128/0.3	–[12]	1715, 1635, 1610	5.03 (br t, J = 6 Hz); 5.5 (br s); 5.6 (br s); 5.8–6.4 (m); 7.54 (d, J = 15 Hz)	67	100

[a] Recorded on Perkin-Elmer 781 instrument.
[b] Recorded on Varian T-60 spectrometer. Only relevant peaks related to the geometry of double bonds are listed.
[c] In $CDCl_3$.
[d] Microanalysis for TLC (silica gel; benzene) purified **4e**: $C_{12}H_{18}O_2$ (194.3) calc. C 74.19 H 9.34. found 74.25 9.05

Table 2. Dienoic Acids **5a–g** and Phenolic Acetates **6a–g** Prepared

Dienoic Acid	Yield (%)	m.p. (°C) or b.p. (°C)/torr found	reported	Phenolic Acetate	Yield (%)	b.p. (°C)/torr found	reported	Recovered Dienoic Acid	
								Dienoic Acid	Recovery (%)
5a	88	134	134.5[19]	**6a**	61	99/25	75–76/8[19]	**5a**	20
5b	95	100/25	119–120/10[20]	**6b**	55	120/25	89/10[19]	**5b**	30
5c	93	109	113[21]	**6c**	65	115/25	212/760[19]	**5c**	22
5d	>95	77–80	93[a,22]	**6d**	90	143/25	120/11[24]	**5d**	3
5e	>95	65	–	**6e**	93	150/1	–[18]	–	–
5f	90	140/5	–	**6f**	60	139/25	131/21[19]	**6f**	35
5g	93	130/0.2	–[23]	**6g**	70	130–35/0.5	–[13,14]	**5g**	20

[a] For 100% *E*-isomer.

3-Methyl-6-(6-methyl-5-hepten-2-yl)-2,4-hexadienoic Acid (5g); Typical Procedure:

The ester **4g** (1.5 g, 6 mmol) is stirred at room temperature with a mixture of 10% aqueous potassium hydroxide (60 ml) and methanol (15 ml) for about 12 h. The mixture is carefully acidified with 10% cold dilute hydrochloric acid (150 ml) and the precipitated acid is extracted with ether (3 × 50 ml).The combined ethereal extract is washed with water (2 × 30 ml) and dried with sodium sulfate. Removal of the solvent gives spectroscopically pure **5g**; yield: 1.3 g (93%) (Table 2).

5-Methyl-2-(6-methyl-5-hepten-2-yl)phenyl acetate, (R)-(−)-Curcuphenol Acetate (6g); Typical Procedure:

A mixture of the 2,4-dienoic acid **5g** (1 g, 4.2 mmol), freshly fused sodium acetate (2 g) and freshly distilled acetic anhydride (25 ml) is stirred under reflux for about 30 h. Most of the acetic anhydride is removed under reduced pressure and saturated aqueous sodium hydrogen carbonate (100 ml) is added to the residue. The mixture is stirred for 1 h and extracted with ether (4 × 30 ml). The combined ether extract is washed with saturated aqueous sodium hydrogen carbonate (50 ml), water (2 × 50 ml) and dried with sodium sulfate. The IR and ^{1}H-NMR spectra of the crude product show the presence of acetate **6g** and the mixed anhydride of the acid **5g** and acetic acid. On column chromatography of the crude product over silica gel (petroleum ether/benzene, gradient elution), acetate **6g** is eluted first; yield: 1.1 g (70%), followed by acid **5g**; yield: 0.2 g (20%) (Table 2).

(R)-(−)-Curcuphenol Acetate (**6g**); $[\alpha]_D^{30}$ −10° (c = 10, $CHCl_3$) (Ref.,[13] $[\alpha]_D^{24}$ −11°; Ref.,[14] $[\alpha]_D^{22}$ −9.6°).

IR ($CHCl_3$): ν = 1750, 1620, 1570 cm^{-1}.

^{1}H-NMR (CCl_4/TMS): δ = 1.13 (d, J = 7 Hz, 3H, $CHC\underline{H}_3$); 1.48 (br s, 3H, olefinic $C\underline{H}_3$); 1.63 (br s, 3H, olefinic $C\underline{H}_3$); 2.2 (s, 3H, $OCOC\underline{H}_3$); 2.28 (s, 3H, $ArC\underline{H}_3$); 2.67 (m, 1H, $C\underline{H}CH_3$); 4.98 (br t, J = 7 Hz, 1H, C=CH); 6.65 (br s, 1H, 6-H_{arom}); 6.83 (dd, J_1 = 8, J_2 = 1.5 Hz, 1H, 4-H_{arom}); 7.02 ppm (d, J = 8 Hz, 1H, 3-H_{arom}).

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