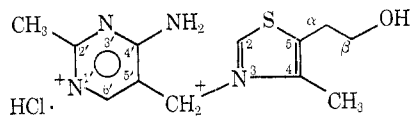
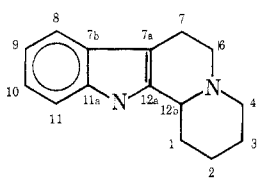
Table I
^{13}C Nmr Data for Thiamine Hydrochloride[a]



	Chemical shift[b]	CH_3OH–H_2O[c] T_1	NOE	T_1^{DD}[e]	CD_3OD–D_2O[c] T_1	NOE	T_1^{DD}[e]	ΔT_1^{DD}, %[d]
Pyrimidine Ring								
C-2′	163.78	4.7	1.7	5.5	7.1	1.3	10.9	+98
C-4′	164.18	4.2	1.7	4.9	9.8	1.0	19.6	+300
C-5′	106.50	4.7	1.8	5.2	4.5	1.9	4.7	−10
C-6′	146.44	0.37	2.0	0.37	0.31	2.1	0.31	−16
2′-CH_3	21.93	1.2	2.1	1.2	0.8	1.9	0.8	−33
Thiazole Ring								
C-2	155.28	0.30	2.0	0.30	*f*	*f*		
C-4	143.62	6.2	1.8	6.9	6.9	1.6	8.6	+25
C-5	137.30	6.4	1.9	6.7	6.4	1.9	6.7	0
5-α-CH_2	30.34	0.37	2.2	0.37	0.32	2.0	0.32	−14
5-β-CH_2	61.04	0.34	2.1	0.34	0.34	1.9	0.36	+6
4-CH_3	12.20	1.2	2.1	1.2	0.85	2.0	0.85	−29
Bridging CH_2								
	50.96	0.28	2.0	0.28	0.24	2.0	0.24	−14

[a] 1.2 *M* in stated solvent systems, 25.2 MHz, 38 ± 3°. [b] In parts per million downfield from TMS (internal dioxane δ 67.40). [c] 1:1 methanol–water solvent (see text). Estimated errors: T_1 (sec) ±5–10%, NOE (η) ±0.1–0.2, T_1^{DD} (sec) ±10–20%. [d] $\Delta T_1^{DD} = [T_1^{DD}$ (partially deuterated) $- T_1^{DD}$ (protio)$]/T_1^{DD}$ (protio) × 100. [e] T_1^{DD} calculated from $(T_1)(1.99)$/NOE observed. Experimental NOE's are given but (physically impossible) NOE's larger than 2.0 were not used in calculations of T_1^{DD}; instead 2.0 was used in those cases. [f] Not measured.

We are using this technique to confirm ^{13}C nmr spectral assignments for other natural products. For example, in the alkaloid below, spectral assignments for the nonprotonated olefinic carbons were confirmed by deuteration at carbons 7 and 12b.[6]



Dideuteration at C-7 increased T_1 for the resonance assigned to carbon 7a by *ca.* 100% while the other nonprotonated carbon T_1's were increased by only 30–40%. Deuterium substitution at 12b lengthened the 12a carbon T_1 by 45% while not appreciably affecting the other carbons (all T_1's were predominantly dipolar).

Experimental Section

The T_1 values in Table I were obtained with an inversion–recovery pulse sequence. Both direct and indirect NOE's were obtained; the values reported in Table I are averages of several runs. Direct NOE's were measured on ^1H decoupled spectra using pulse-modulated decoupling. NOE's of 1.7–1.8 indicate minor but probably significant contributions from other relaxation mechanisms.

In the pulse-modulated $\{^1H\}$ experiments, ^{13}C pulse intervals > ~$4T_1$ for all carbons were used. Wideband $\{^1H\}$ decoupling (*ca.* 15 W) was gated on *only* during tha data acquisition periods (typically 0.8 sec). The nuclear Overhauser effect does not grow in during an individual free induction decay acquisition, even if T_1 is much less than 1 sec (*e.g.*, for the protonated CH and CH_2 carbons); the long delays between pulses eliminate previously generated NOE through ^{13}C–^1H relaxation processes.

Registry No.—Thiamine hydrochloride, 67-03-8.

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(1) (a) General Electric Visiting Professor, summer 1973. (b) Address this author: Department of Chemistry, Florida State University, Tallahassee, Fla. 32306.

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The Specific Introduction of an Isopropylidene Group in the Synthesis of the Monoterpene Terpinolene and the Sesquiterpene (±)-α-Curcumene

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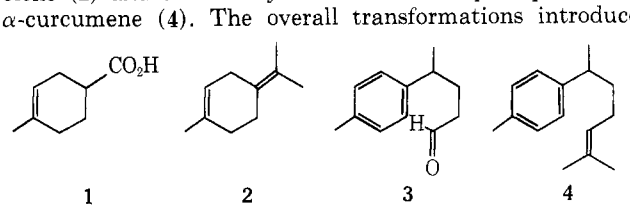
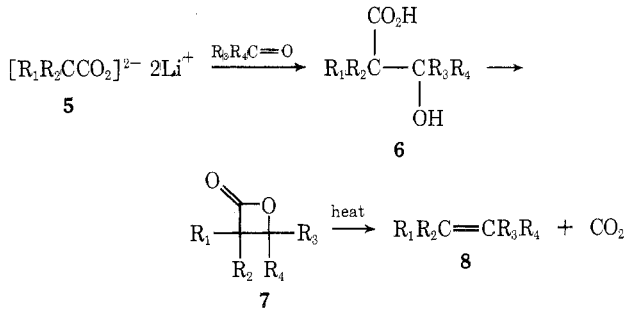
The isopropylidene group is a commonly occurring structural feature found in naturally occurring products.[2] In order to demonstrate the application of a simple procedure for the introduction of this grouping in synthetic routes to natural products, we wish to report the conversions of the carboxylic acid **1** into the monoterpene terpinolene (**2**) and the aldehyde **3** into the sesquiterpene (±)-α-curcumene (**4**). The overall transformations introduce



1 **2** **3** **4**

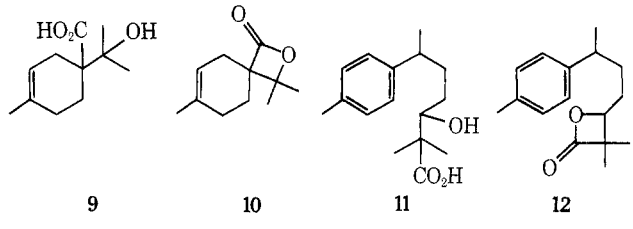
Scheme I



an isopropylidene group either (1) at a position bearing a carboxyl group or (2) at a position bearing a carbonyl group.

The steps involved in these transformations are outlined in Scheme I. Treatment of lithium salts of α-lithio carboxylic acids **5** with carbonyl substrates yields β-hydroxy acids **6**.[3] These β-hydroxy acids can be cyclized to β-lactones **7**, which on thermolysis readily lose CO_2 to yield olefins **8** with introduction of a double bond at a specific position.[4]

Terpinolene. Terpinolene (**2**) has been previously synthesized *via* a [4 + 2] cycloaddition of isoprene and dimethylallene.[5] In our synthetic route the desired carboxylic acid **1** was prepared by a Diels–Alder cycloaddition of isoprene and acrylic acid. The lithium α-lithio carboxylate salt of **1** was prepared by treatment of **1** with 2 equiv of lithium diisopropylamide in THF and this α anion was treated with acetone to yield the β-hydroxy acid **9** (65%). This acid **9** was converted to β-lactone **10** (82%) by treatment at 0° with benzenesulfonyl chloride in pyridine. Thermolysis of β-lactone **10** at 140° (3 hr) led to terpinolene (**2**, 93%).



9 **10** **11** **12**

(±)-α-Curcumene. The synthesis of (±)-α-curcumene has previously been accomplished by treatment of aldehyde **3** with isopropylidenetriphenylphosphorane.[6] Other routes to this sesquiterpene have also been reported.[7] Aldehyde **3**[8] was the starting material for the present synthesis. The lithium α-lithio carboxylate salt of isobutyric acid was generated by treatment of isobutyric acid with 2 equiv of lithium diisopropylamide. Aldehyde **3** was added to this α anion to produce the β-hydroxy acid **11** (73%). This acid was converted to β-lactone **12** (77%) by treatment with benzenesulfonyl chloride in pyridine. The β-lactone was thermally decarboxylated at 140° (3 hr) to yield the racemic sesquiterpene (±)-α-curcumene (90%).

It appears that this method should find general use for the specific introduction of double bonds in natural product syntheses. It should prove a good alternative to the Wittig reaction or some more complicated procedure for introducing an isopropylidene group.[9]

Experimental Section

All melting points are uncorrected. The ir spectra were recorded using a Perkin-Elmer 237B spectrophotometer. The nmr spectra were recorded on a JEOL MH-100 using TMS as an internal standard. Microanalyses were performed by Robertson Laboratory, Florham Park, N. J. 07932.

4-Methyl-3-cyclohexenecarboxylic Acid (1). Isoprene (2.7 g, 40 mmol) and acrylic acid (2.8 g, 40 mmol) were heated in a sealed tube at 100–110° for 24 hr. After cooling, the solid was recrystallized from hexane–chloroform to yield a white solid: mp 96–97° (lit.[10] mp 99°); ir ($CHCl_3$) 3100 and 1700 cm^{-1}; nmr ($CDCl_3$) δ 1.7 (s, 3 H, $-CH_3$), 1.8–2.4 (m, 6 H, $-CH_2-$), 2.4–2.7 (m, 1 H, $-CHCO_2H$), 5.5 (broad, 1 H, =CH-), and 11.9 ppm (s, 1 H, $-CO_2H$).

β-Hydroxy Acid 9. Lithium diisopropylamide was prepared by dissolving 2.02 g (20 mmol) of diisopropylamine in 50 ml of THF under nitrogen and adding 10.5 ml (20 mmol) of 1.9 *M* *n*-butyllithium in hexane at −40°. The mixture was stirred for 20 min below 0° and recooled to −40°, and 1.42 g (10 mmol) of **1** was added while keeping the temperature below −20°. The reaction was heated at 50° for 2 hr and again cooled to −40°, and 0.58 g (10 mmol) of acetone was added. The reaction was stirred for an additional 2 hr, poured over 100 g of ice, and extracted with 4 × 25 ml of ether. The aqueous phase was acidified with 3 *N* HCl, extracted with 4 × 25 ml of ether, and dried over $MgSO_4$, and the solvent was removed at reduced pressure. This yielded 1.3 g (65%) of a solid, fractionally recrystallized from pentane: mp 67–69°; ir ($CHCl_3$) 3450, 3100, and 1700 cm^{-1}; nmr ($CDCl_3$) δ 1.3 [s, 6 H, $(CH_3)_2COH$], 1.7 (s, 3 H, $CH_3C=$), 1.6–2.8 (m, 6 H, $-CH_2-$), 5.5 (m, 1 H, HC=C), and 8.6 ppm (broad, 2 H, -OH and $-CO_2H$). This material was not purified further.

β-Lactone 10. The crude β-hydroxy acid **9** (0.80 g, 4.0 mmol) was dissolved in 40 ml of anhydrous pyridine and cooled to −5°. To the stirred mixture 2.15 g (12.0 mmol) of $PhSO_2Cl$ was added, and the mixture was held at 0° for 18 hr, poured over 100 g of ice, and extracted with 5 × 25 ml of ether. The organic phase was washed with 2 × 50 ml of saturated $NaHCO_3$, dried over $MgSO_4$, and stripped at reduced pressure (0.5 mm to remove pyridine). This yielded 0.59 g (82%) of a solid which was recrystallized from pentane: mp 36–37°; ir (neat) 1810 cm^{-1}; nmr ($CDCl_3$) δ 1.50 and 1.53 [s, each 3 H, $(CH_3)_2CO$], 1.7 (s, 3 H, $CH_3C=$), 1.8–2.4 (m, 6 H, $-CH_2-$), and 5.4 ppm (broad, 1 H, HC=C).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.27; H, 8.78.

Terpinolene (2). The β-lactone **10** (0.4 g, 2.2 mmol) was heated at 140° for 3 hr. The resulting liquid was distilled at 100° (18 mm) to yield 0.28 g (93%) of **2**: $n^{25}D$ 1.4891; ir (neat) 2980, 2920, 1440, and 1370 cm^{-1}; nmr ($CDCl_3$) δ 1.68 (broad, 9 H, $CH_3C=$), 2.0 (m, 2 H, $-CH_2C=$), 2.3 (m, 2 H, $-CH_2C=$), 2.8 (m, 2 H, $=CCH_2C=$), and 5.45 ppm (m, 1 H, HC=).[11]

Anal. Calcd for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 88.55; H, 11.69.

β-Hydroxy Acid 11. The identical procedure used for the formation of the β-hydroxy acid **9** was performed on 0.5 g (5.7 mmol) of isobutyric acid using 1.0 g (5.7 mmol) of aldehyde **3** as the electrophile. This yielded 1.1 g (73%) of an oil which was used without further purification: ir (neat) 3420, 3150, and 1700 cm^{-1}; nmr ($CDCl_3$) δ 1.1–1.4 (m, 9 H, CH_3-), 1.5–2.8 (m, 5 H, $-CH_2-$ and CH_3CH-), 2.4 (s, 3 H, CH_3Ar), 3.7 (m, 1 H, HCOH), and 7.2 ppm (s, 4 H, ArH).

β-Lactone 12. The same procedure used to make β-lactone **10** was run on 0.7 g (2.7 mmol) of **11** using 1.4 g (8.0 mmol) of $PhSO_2Cl$. This yielded an oil which was decolorized in pentane with carbon to yield 0.49 g (77%) of a clear liquid **12**: ir (neat) 1820 cm^{-1}; nmr ($CDCl_3$) δ 1.05–1.4 (m, 9 H, CH_3-), 1.4–2.8 (m, 5 H, $-CH_2-$ and CH_3CH-), 2.36 (s, 3 H, CH_3Ar), 4.2 (m, 1 H, HCO-), and 7.2 ppm (s, 4 H, ArH).

Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.85; H, 8.77.

(±)-α-Curcumene (4). In a microdistillation apparatus, 0.3 g (1.2 mmol) of the β-lactone **12** was heated to 140° (760 mm) for 3 hr. The bath temperature was raised to 160° and the oil **4** was molecularly distilled, giving 0.22 g (90%) of a clear liquid: uv ($CHCl_3$) 261, 267, and 274 nm; ir (neat) 3100, 3060, 3030, 2970, 2930, 2880, 1510, 1450, 1375, and 810 cm^{-1}; nmr ($CDCl_3$) δ 1.2 (d, 3 H, J = 7 Hz, CH_3CH-), 1.54 (s, 3 H, $CH_3C=$), 1.68 (s, 3 H, $CH_3C=$), 1.4–2.1 (m, 4 H, $-CH_2-$), 2.36 (s, 3 H, CH_3Ar), 2.7 (m, 1 H, CH_3CH-), 5.18 (t, 1 H, HC=C), and 7.2 ppm (s, 4 H, ArH); $n^{25}D$ 1.4993. The physical and spectral data are consistent with those in the literature.[12]

Registry No.—**1**, 4342-60-3; **2**, 586-62-9; **3**, 3241-74-5; **4**, 3649-81-8; **9**, 50987-52-5; **10**, 50987-53-6; **11**, 50987-54-7; **12**, 50987-55-8; isoprene, 78-79-5; acrylic acid, 79-10-7.

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Communications

Facile Reaction of Potassium Hydride with Ketones. Rapid Quantitative Formation of Potassium Enolates from Ketones *via* Kaliation[1]

Summary: In contrast to lighter saline hydrides, KH in tetrahydrofuran vigorously metalates a wide range of ketones with little or no self-condensation or reduction; solutions of highly reactive potassium enolates are formed quantitatively in minutes at 20°.

Sir: Potassium hydride in ethereal solvents exhibits exceptional reactivity toward weak carbon acids such as fluorene (pK_A = 23), methyl *tert*-butyl ketone (pK_A = 20.8), and indene (pK_A = 19), in marked contrast to the sluggishness or inertness of lighter saline hydrides (NaH and LiH). Of particular interest is the metalation of ketones; quantitative formation of highly reactive potassium enolates requires only minutes at room temperature even with relatively hindered structures. Pure solutions of the enolates—free of ketone by ir—are obtained by decantation.

Ketone enolates are versatile reactive intermediates of interest as probes of cation solvation and ion pairing in ambient ions,[2] in formation of carbon–carbon bonds in synthesis,[3] and as ligands of transition metals.[4] Formation of enolates from ketones has been accomplished recently by a variety of methods[5-12] with lithium as the cation in the great majority of cases. Only occasionally have saline hydrides been employed[13,14] despite their attractive simplicity: they are insoluble in nonreacting organic solvents and are readily separated; the sole by-product of metalation is hydrogen gas; and hydrides are both readily available and indefinitely stable. Unfortunately, reaction of LiH and NaH with unactivated ketones has proven exceptionally sluggish. Even a relatively acidic ketone—butyrophenone—has been reported to require several days at 35° (ether solvent) for complete metalation by NaH.[13a] Metalation by NaH is also complicated by considerable self-condensation of the ketone.[14]

KH[16a] is far more reactive than LiH[16a] or NaH[16a] toward ketones in tetrahydrofuran (THF), as illustrated in Figure 1 in metalation of methyl *tert*-butyl ketone (pinacolone). This enhanced reactivity is *not* an artifact of the degree of dispersion of solid KH; even particularly finely divided NaH (sedimentation rate in pentane <0.1 times that of KH) reacts much more sluggishly.

Metalation is readily accomplished by addition of the ketone to a vigorously stirred suspension of KH in anhydrous THF at 20°; hydrogen evolution commences immediately and is very vigorous. In a typical example 25 mmol of pinacolone was metalated in 5 min by 28 mmol of KH suspended in 40 ml of THF, the bulk of the hydrogen being evolved in <2 min. The clear supernatant solution showed 0–1% ketone in several runs by ir analysis.[17] The 1710-cm^{-1} absorption (C=O stretch) disappears upon metalation and is replaced by a strong absorption at 1568 cm^{-1}. Glpc analysis of a sample quenched in a mixture of ether and 1.0 *M* HCl showed 100% recovery of ketone. Addition of excess triethylamine and trimethylchlorosilane[5] to the reaction mixture at −78° yielded >98% trimethylsilyl enol ether.

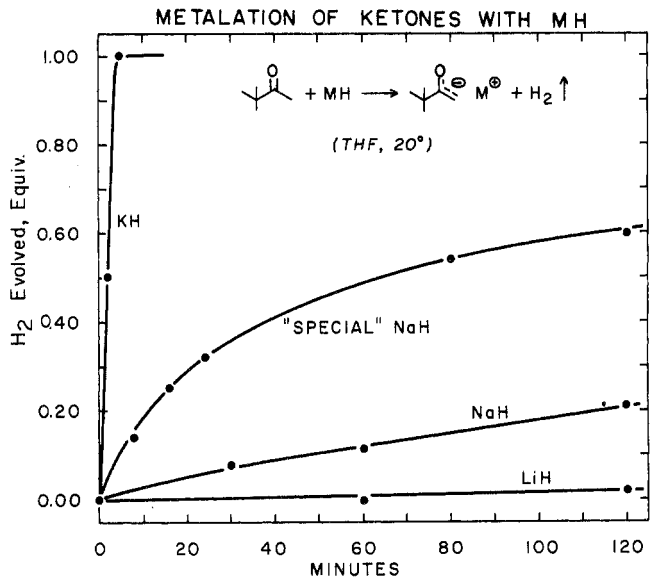

Figure 1. Metalation of pinacolone in tetrahydrofuran (0.5 *M*) with excess saline hydrides. "Special NaH" was a sample of particularly finely divided NaH obtained from Ventron Corp.[16b] Other hydrides are standard commercial products of Alfa Products Div. of Ventron Corp.

Similar results were obtained with a variety of ketones including those labile toward self-condensation, as shown in Table I. No reduction of the carbonyl group by KH was observed.[18] Unsymmetrically substituted ketones yield directly equilibrium mixtures of enolates.

Potassium enolates are highly reactive. Thus the enolate of 2,4-dimethyl-3-pentanone reacts with excess methyl iodide in 5 min at −78°; a 50:1 ratio of mono to dialkylated products is formed.[19]

In the absence of excess ketone, potassium enolates do not equilibrate; however, the highly reactive enolates may be equilibrated readily in the presence of small amounts of free ketone even at −78° to yield enolate mixtures enriched in the more stable component. Thus 3-methyl-2-butanone is metalated to yield an equilibrium mixture of enolates containing 88% *less* substituted isomer at 20°; no