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Synthetic Studies on the Sesquiterpenoids in Nature: ar-Turmerone, α-Curcumene, Nuciferal

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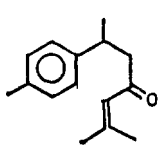
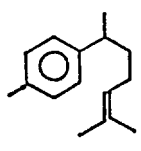
ar-Turmerone(**1**), α-curcumene(**2**), and nuciferal(**3**) are structurally related aromatic sesquiterpenic compounds in nature. The kefonic sesquiterpene **1** was obtained as the chief component of the essential oil of turmeric[1,2], and the sesquiterpenic hydrocarbon **2** was first detected as a constituent of the essential oil from the rhizomes of *Curcuma aromatica* Salisb by Simonsen *et al.*[3] The aldehydic sesquiterpene **3** was separated as a consitituent of the volatile oil from the wood Torreya Nucifera[4], and the structure bears a resemblance to that of sinenals[5] which has to do with the orange flavors.

In previous papers, a number of syntheses of **1**[6-13], **2**[14-16], and **3**[17-23] have been reported independently. In the present work, we have been interested in convenient syntheses of these three terpenoids in a synthetic procedure; the synthesis of **1**, the conversion of **1** into **2**, and then into **3** successively.



1



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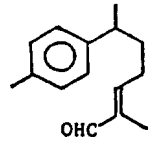


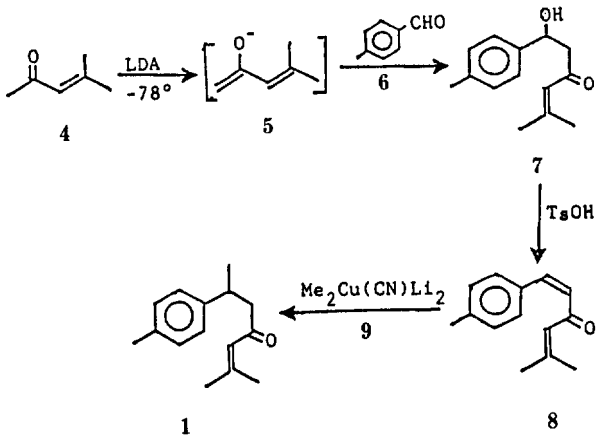
3

The α,β-unsaturated ketone **1** was synthesized by modifying the Garcia-Maldonado's procedure[8], as shown in Scheme 1: A freshly prepared n-butyllithium, obtained by the reaction of lithium shavings (2.3 g, 320 mmol) with n-butyl bromide (22 g, 160 mmol) in anhydrous ether (85 m*l*) under nitrogen, was added at 0 °C to a solution of diisopropylamine (12 g, 120 mmol) in tetrahydrofuran (120 m*l*) to give lithium diisopropylamide(LDA). To this solution, cooled to -78 °C, was added dropwise with stirring a solution of mesityl oxide (**4**, 10.8g, 110 mmol) in tetrahydrofuran (30 m*l*) to give a kinetically controlled enolate ion **5**, followed by the addition of a solution of *p*-tolualdehyde (**6**, 12.0g, 100 mmol). The hydrolytic work-up and chromatography afforded a ketonic alcohol **7** in 75% yield, which showed IR(neat) bands at 3450 (OH), 1680(C = O), 1620(C = C), 1515(arom. C = C), 1450, and 820 cm^{-1}, and ^{1}H-NMR($CDCl_3$) signals at δ7.2(s $4H_{arom}$), 6.05(m, 1H, vinylic), 5.1(m, 1H, ArCH), 3.7(d, 1H, OH), 2.8(d, 2H, O = CCH_2), 2.3(s, 3H, $ArCH_3$), 2.15(s, 3H, *cis* allylic CH_3), 1.85(s, 3H *trans* allylic CH_3).

The dehydration of the ketonic alcohol **7** was carried out by refluxing it with *p*-toluenesulfonic acid in benzene in a flask fitted with a Dean-Stark trap for 2 hr, to give 85% yield of a dienone **8**, yellow needles (m.p. 77-78 °C), which showed IR(KBr) bands at 1680(w), 1655(w), 1640(C = O), 1600(arom. C = C), 1510, 810 cm^{-1}, and ^{1}H-NMR($CDCl_3$) signals at δ7.5 (d, 1H, CH = C-C = O, J = 16 Hz), 7.3(m, $4H_{arom.}$), 6.7(d, 1H, CH-C = O, J = 16 Hz), 6.3(m, 1H, Me_2C = CH), 2.3(s, 3H, $ArCH_3$), 2.2(s, 2H, *cis* CH_3), 1.9(s, 3H, *trans* CH_3).

The Michael addition of methyl group to the dienone **8** was accomplished by the reaction of lithium cyanodimethyl cuprate(**9**)[24] with **8**, to give a regioselective conjugate addition product ar-turmerone(**1**). When lithium dimethylcuprate[25,26] was used instead of $Me_2Cu(CN)Li_2$(**9**), not only longer reaction time was needed (10 min. to 2 hr), but also the yield was reduced (70% to 50%). Thus, a freshly prepared methyllithium, obtained from lithium shavings (1.25g, 180 mmol)

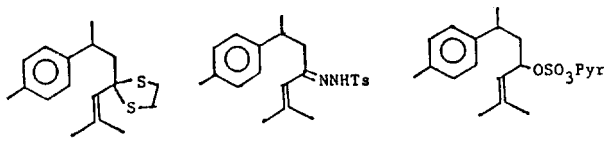
and methyl iodide (10.5g, 74 mmol) in dry ether (50 m*l*), was added by cannulation at −5 °C under nitrogen, to a suspension of cuprous cyanide (2.69g, 30 mmol) in dry ether (20 m*l*) to form a tan solution, followed by the addition of an etherial solution of the dienone 8(2.0g, 10 mmol). The aqueous workup and chromatography on silica gel furnished a yellow liquid (1.5g, 70% yield) of α,β-unsaturated ketone **1**, which showed IR(neat) peaks at 3020, 1690(C = O), 1620(C = C), 1515 (arom. C = C), 1450, 1380, 815 cm^{-1}, ^{1}H-NMR(CCl_4) signals of δ7.05(s, $4H_{arom}$), 6.0(m, **1H**, vinylic), 3.3(m, 1H, ArCH), 2.65(d, 2H, O = CCH_2), 2.3(s, 3H, $ArCH_3$), 2.1(s, 3H, *cis* CH_3), 1.8(s, 3H, *trans* CH_3), 1.2(d, 3H, $ArCCH_3$), and MS (*m/e*) value of 216(M^+).



Scheme 1

The conversion of **1** into **2** is a most important step in this investigation, since the effective reduction of carbonyl group in α,β-unsaturated ketone to methylene group, without migration of double bond, has never been thoroughly investigated to date[27]. We have examined the direct reduction of **1** to **2**: The Clemmensen reduction afforded a mixture of products formed by the attack of both functions[28], double bond and carbonyl group. A mild Wolff-Kishner reduction[29] yielded a complicated mixture containing trace amount of hydrocarbon fraction. Direct reduction of **1** to **2** was impossible by known method. Thus, this conversion was tried by Mozingo reduction, which involves the reaction of **1** with 1,2-ethanedithiol in the presence of BF_3 to give 85% yield of dithioketal **10**, followed by the gentle desulfurization of **10** by refluxing with an excess of Raney nickel[30,31] in ethanol. This reduction was accompanied not only by a double bond shift, but also by the attack of aromatic ring, giving no encouraging result. Reduction of the *p*-toluenesulfonylhydrazone(**11**) of **1** with sodium borohydride[32,33] or cyanoborohydride[34] is also accompanied by a double bond shift, and is not proper for this purpose.

We performed another experiment for the conversion of **1** into **2**, which involves the reduction of **1** to corresponding allylic alcohol **12** (Scheme 2), followed by deoxygenation of the alcohol into an alkene. The α,β-unsaturated ketone **1** was reduced with lithium aluminum hydride in ether to give **12** in 85% yield. The allylic alcohol **12** was then treated with pyridine–sulfur trioxide complex in tetrahydrofuran, followed by reduction of the intermediate sulfate monoester **13**, without separation, with lithium aluminum hydride, to yield never **2**. Though Corey *et al.*[35], by this procedure, achieved the deoxygenation of allylic primary alcohol to corresponding olefin without saturation or a shift of the double bond, the allylic secondary alcohol **12** could not be deoxygenated to corresponding olefin **2** because of rearrangement of double bond.



10 **11** **13**

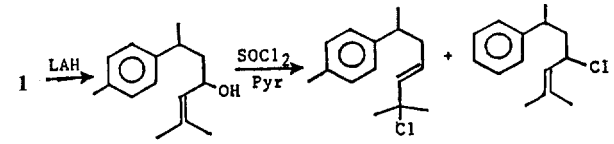
A conversion of the allylic alcohol **12** into corresponding olefin **2** was achieved by conversion of **12** into chloride, followed by the reduction of the chloride, as shown in Scheme 2. To a mixture of **12**(436 mg, 2 mmol) and pyridine (174 mg, 2.2 mmol) in ether (10 m*l*) cooled to 0 °C, was added dropwise a solution of thionyl chloride (250 mg, 2.1 mmol) in ether (5 m*l*), followed by stirring for 3 hr at room temperature. The reaction mixture was poured into cold water (20 m*l*), extracted with ether, washed with aqueous ammonium chloride and water, and dried over anhydrous magnesium sulfate. A careful evaporation of the solvent in vacuo afforded a colorless liquid of crude tertiary chloride **14a** which showed the ^{1}H-NMR($CDCl_3$) signals at δ7.01(s, $4H_{arom}$), 6.1–5.3(m, 2H, vinylic), 2.8(m, 1H, ArCH), 2.3(s, 3H, $ArCH_3$), 1.8(t, 2H, allylic), 1.6(s, 6H, $ClCMe_2$), and 1.2(d, 3H, $ArCCH_3$).

The crude **14a** was so sensitive to heat and silica gel that it was hard to handle. In some cases, it changed promptly to purple during the evaporation of solvent, after workup, at reduced pressure, even in the room temperature. Thus, the crude **14a** was reduced, without purification, with lithium aluminum hydride (38 mg, 1 mmol) in ether for 12 hr at room temperature. An ordinary workup and chromatography furnished a colorless liquid which was known to be a mixture of isomeric olefins **2** and **2'**. The yield of the isomeric mixture was 79% based on the allylic alcohol **12**. The ^{1}H-NMR spectrum of the mixture showed very similar signals to that of pure **2**(vide infra) obtaind from the another synthetic route (Scheme 3), but it has an added doublet at δ0.95 which was responsible for two methyl groups of isopropyl moiety in the isomer **2'**. The gas chromatographic analysis indicated that the mixture consisted of 77% of **2** and 23% of **2'**.

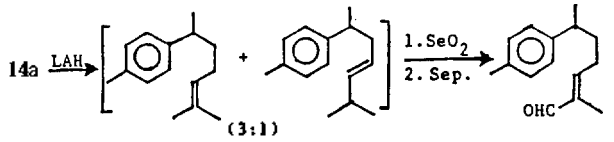
Whatever the exact mechanism of reaction, the products of the foregoing reactions showed that allylic rearrangement has taken place in both reactions; conversion of allylic alcohol into chloride and reduction of the chloride to olefin. The two regioselective reactions afforded the desired products which have been expected with regard to the previous literature[36].

The gem-dimethyl olefin **2** could be oxidized to a transaldehyde **3** by following the Bhalerao and Rapoport work[37]. However, as the separation of the mixture (2 + 2') was very difficult by usual chromatography, the mixture was used in next experiment without separation: The isomeric mixture (303 mg, 1.5 mmol) and selenium dioxide (333 mg, 3 mmol) was refluxed in 95% ethanol (30 m*l*) for 12 hr. After workup, the crude oxidation product was chromatographed on silica gel to give yellowish liquid (136 mg) of nuciferal(**3**), which showed IR(neat) frequencies at 3020, 2820 and 2710(CHO),

1690(C = O), 1645(C = C), 1515(arom. C = C), 1450, 1380, 820 cm^{-1}, ^{1}H-NMR($CDCl_3$) signals at δ9.3(s, 1H, CHO), 7.1(s, $4H_{arom.}$), 6.4(t, 1H, J = 7 Hz, vinyl), 2.7(m, 1H, ArCH), 2.3(s, 3H, $ArCH_3$), 2.2-1.6(m, 4H, allylic CH_2), 1.7(s, 3H, *cis* CH_3), 1.2(d, 3H, $ArCHCH_3$), and MS(*m/e*) value of 216(M^+).



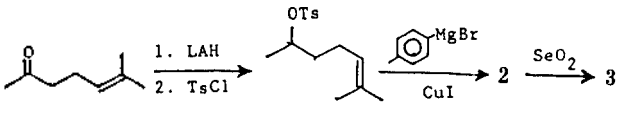
12 14a major 14b trace



2 2' 3

Scheme 2

The pure α-curcumene(**2**), as mentioned above, was prepared by another route (Scheme 3) in order to compare it with the reduction product of the tertiary chloride **14a**. 6-Methyl-5-hepten-2-one(**15**) was reduced with lithium aluminum hydride in ether to 6-methyl-5-hepten-2-ol(**16**) in almost quantitative yield. A mixture of the olefinic alcohol **16**(2.56g, 20 mmol), pyridine (30 m*l*) and *p*-toluenesulfonyl chloride (7.62g, 40 mmol) was stirred for 48 hr at room temperature. After workup, the crude product was chromatographed on silica gel to give 4.6g (81% yield) of the tosylate ester **17**. A Grignard reagent, prepared from *p*-bromotoluene (5.2g, 30 mmol) and magnesium turnings, was added by cannulation to a solution of **17**(2.82g, 10 mmol) and copper(I) iodide(0.9g, 5 mmol) in THF(80 m*l*), followed by gentle reflux for 12 hr. Work-up and chromatography afforded 63% yield of α-curcumene(**2**), which showed IR(neat) bands at 3050, 3020, 2960, 2920, 1515 (arom. C = C), 1375, 815 cm^{-1}, ^{1}H-NMR ($CDCl_3$) signals at δ7.1(s, $4H_{arom.}$), 5.1(t, 1H, vinylic), 2.7(m, 1H, ArCH), 2.3(s, 3H, $ArCH_3$), 1.7(s, 3H, allylic CH_3), 1.5(s, 3H, allylic CH_3), 1.2(d, 3H, CH_3), and MS(*m/e*) value of 202 (M^+).



15 17 18

Scheme 3

The coupling of the tosylate ester **17** with *p*-tolylmagnesium bromide(**18**) was promoted by the addition of copper(I) iodide, to give 46-63% of coupling product **2**, whereas the yield was decreased to 10%[38] in the absence of the copper(I) iodide. Oxidation of pure gem-dimethyl olefin with selenium dioxide furnished 64% yield of *trans*-aldehyde **3**.

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Synthesis of Functional Derivatives of 1,2-Bisbenzylbenzene

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We have been interested in the syntheses of functional derivatives of dibenzoylbenzenes and dibenzylbenzenes, since they are of considerable utility in organic synthesis, particularly as synthetic intermediates in the synthesis of new carbonyl host molecule. In recent communication[1] we reported general synthetic routes for the derivatives of dibenzoylbenzenes in which functional groups are introduced to every position of benzoyl group. In the present investigation, we wish to provide practical syntheses of 1,2-bis(2-functionalbenzyl)benzenes that are derivatives of 1,2-bisbenzylbenzene in which functional groups are introduced at ortho positions of each benzyl moieties. Some of them are symmetrical 1,2-bisbenzylbenzenes which have same functional groups on each ortho position of benzyl groups, as shown in structure I, and the others are unsymmetrical ones possessing different functional groups on each ortho position of benzyl groups, as shown in structure II.

The symmetrical 1,2-bisbenzylbenzenes I_{a-f}(Table 1) could be synthesized by the cross-coupling of aryl Grignard reagent, prepared from 2-functionalbromobenzene(**1**), with α,α'-dihalo-*o*-xylene(**2**) in the presence of copper(I) salt catalyst (Scheme 1). Without copper(I) salt the coupling reaction

Table 1. Symmetrical 1,2-Bis(2-functionalbenzyl)benzenes I_{a-f}

Products (G)	Reactants	General procedure	yield[a] (%)	m.p.[b] (°C)	MS *m/e*(M$^+$)	IR[c] ν(cm^{-1})	NMR($CDCl_3$, TMS)[d] δ(ppm)
Ia (CH_3)	1a, 2	1	95	65-66	286	3060,3020,2980 2910,1600,1490	7.3-6.8(m, 12H$_{arom.}$) 3.8(s, 4H, benzylic) 2.25(s, 6H, CH_3)
Ib (OCH_3)	1b, 2	1	94	112-113	318	3060,2960,2840 1600,1587,1490 1460,1440,1160 1105	7.2-6.7(m, 12H$_{arom.}$) 3.95(s, 4H, benzylic) 3.75(s, 6H, OCH_3)
Ic (CH_2OH)	1c[e], 2	1	80	115-117	318	3600-3100(broad) 3060,3920,2920 1600,1580,1490 1450,1430	7.5-6.8(m, 12H$_{arom.}$) 4.5(s, 4H, CH_2O) 4.0(s, 4H, $ArCH_2Ar$) 2.2(s, 2H, OH)
Id (Id) (CHO)	1d[e], 2 (Ic)	1 (2)	50 (82)	106-107	314	3060,3010,2830 2730,1700,1600 1575,1490,1450	10.0(s, 2H, CHO) 8.0-6.7(m, 12H$_{arom.}$) 4.35(s, 4H, benzylic)
Ie (OH)	Ib	2	75	108-109	290	3430-3300(broad) 3060,3030,2920 1600,1585,1490 1455,1200,1160	7.2-6.5(m, 12H$_{arom.}$) 5.3(s, 2H, OH) 3.9(s, 4H, benzylic)
If (CH_2Br)	Ic	2	76	118-119	446 444 442	3055,3010,2920 2850,1600,1490 1448	7.5-6.8(m, 12H$_{arom.}$) 4.5(s, 4H, CH_2Br) 4.2(s, 4H, benzylic)

[a]Isolated yield based on α,α'-dibromo-*o*-xylene(**2**). [b]Melting point were not corrected. [c]IR spectra were recorded with Perkin-Elmer Model 782 spectrometer. [d]NMR spectra were recorded on Bruker AC80 FT NMR spectrometer. [e]Protected Ic and Id as THP ether and cyclic acetal respectively.