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Synthesis of bisabolane sesquiterpenes: A Johnson-Claisen rearrangement approach

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Abstracts

Several bisabolane sesquiterpenes, (±)-curcumene, (±)-curcuphenol, (±)-curcudiol and (±)-curcuhydroquinone, have been synthesized in racemic form and fully characterized. The salient characteristic of our approach is that a Johnson-Claisen arrangement was involved as a key step.

Keywords: Bisabolane sesquiterpenes; Johnson-Claisen rearrangement; Synthesis

The aromatic bisabolane compounds are a small family of sesquiterpenes having the simplest monocarbocyclic skeleton which have been popular synthetic targets for 30 years [1]. Typified by the parent hydrocarbons curcumene [2] had been recognized as odor component of many plant essential oils. (+)-Curcuphenol and (+)-curcudiol were firstly isolated from the water collection of the sponge *Didiscus flavus*. (+)-Curcuphenol was found to be an inhibitor of gastric H,K-ATPase and to have antitumor and antifungal activities [3]. (−)-Curcuphenol, (−)-curcuhydroquinone and (−)-curcuquinone were isolated from the Caribbean gorgonian *Pseudopterogorgia rigida* and showed antibacterial activity against *Staphylococcus aureus* and the marine pathogen *Vibro anguillarum* [4]. Curcuhydroquinone and curcuquinone have been used for the synthesis of some heliannuols [5], one kind of allelochemicals isolated from sunflower *Helianthus annuus* leaves bearing significant biological activity. Because of their wide range of biological activities, these compounds and their derivatives are attractive synthetic targets, and especially to verify the usefulness of newly developed synthetic methodology. Although several reports of the synthesis this kind of compounds can be found in literatures, the existent routes are either long or inefficient [6].

Johnson-Claisen rearrangement is a powerful tool in synthesis of naturally occurring products in which a key intermediate of derivatives of δ,ε-unsaturated pentanoic acid was involved [7]. As an extension of our continuous effort to synthesize those kinds of naturally occurring products [8], herein, we wish to report the synthesis of (±)-α-curcumene **1**, (±)-curcuphenol **2**, (±)-curcuhydroquinone **3** and (±)-curcudiol **4** through a Johnson-Claisen rearrangement approach.

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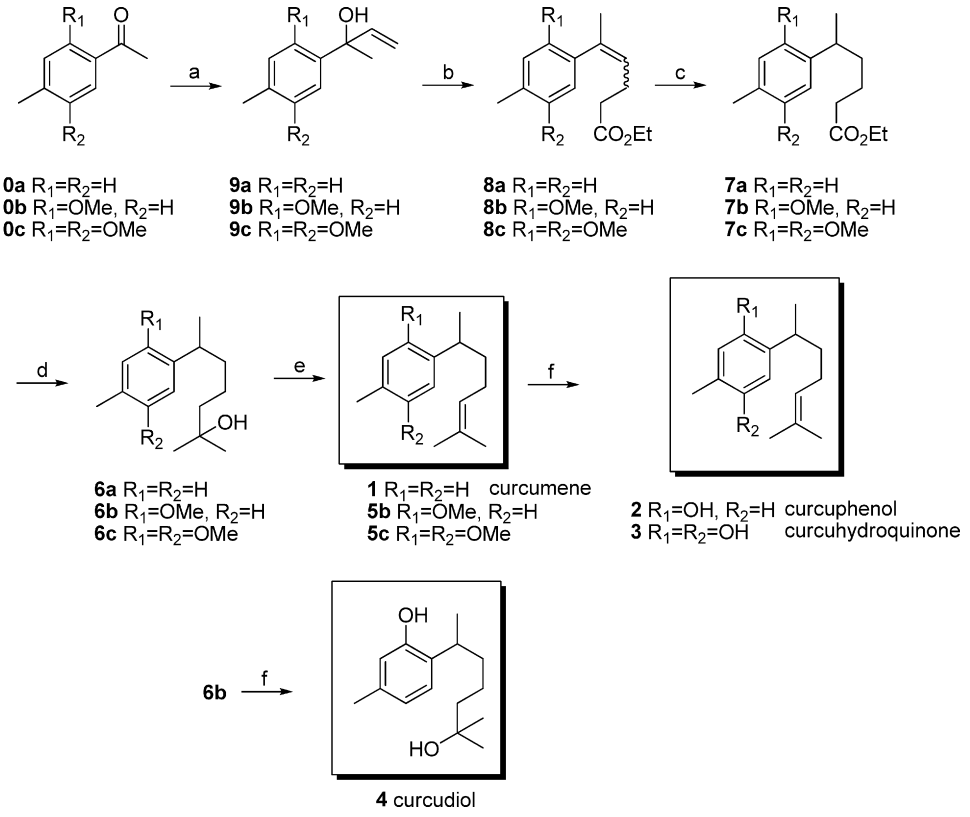

Scheme 1. Reagents and conditions: (a) CH_2═$CHMgBr$, 0 °C–r.t., 85–93%; (b) $CH_3C(OEt)_3$, EtCOOH, 165 °C, 1d, 65–86%; (c) H_2, 5% Pd/C, EtOAc, 92–96%; (d) 4 equiv. MeMgI, THF, 0 °C–r.t., 93–97%; (e) I_2, THF, reflux, 95–98%; (f) EtSNa, DMF, 130 °C, 93–98%.

As shown in Scheme 1, our synthesis commenced at acetophenones **10a**–**10c**, carbinols **9a**–**9c** will be given after a Grignard addition in 85–93% yield. The carbinols underwent a Johnson-Claisen rearrangement at the presence of $CH_3C(OEt)_3$, propanoic acid at 165 °C, to give compounds **8a**–**8c** in good yield. The double bonds were reduced after catalytic hydrogen to furnish **7a**–**7c** in excellent yield. Compounds **7a**–**7c** were subjected to an excess MeMgI addition to afford the tertiary alcohol. (±)-curcudiol **4** was obtained after a demethylation step of compound **6b** using NaSEt in 95% yield. (±)-α-Curcumene **1** was afforded after dehydration of the **6a** by I_2, and dehydrated products **5b** and **5c** were got in very high yield at same conditions, respectively. Compounds **7b**–**7d** can be converted to (±)-curcuphenol **2**, (±)-curcuhydroquinone **3** and using a NaSEt demethylation protocol in 93–98% yield. The spectrums of target molecules are identical to the ones in the literature [9]. It is obvious that our synthetic route is terse and effective.

In summary, we have achieved an effective and facile route to synthesis of (±)-α-curcumene **1**, (±)-curcuphenol **2**, (±)-curcuhydroquinone **3** and (±)-curcudiol **4** in higher yield using cheap starting materials. The Johnson-Claisen rearrangement was used is our salient characteristic of our approach.

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[9] Select spectrum data: Compound **2**, IR (neat): 3537, 2965, 2935, 2866, 1664, 1617, 1421, 808 cm^{-1}. ^1H NMR: 1.22 (d, 3H, J = 7.0 Hz), 1.54 (s, 3H), 1.55–1.69 (m, 2H), 1.68 (s, 3H), 1.89–1.97 (m, 2H), 2.27 (s, 3H), 2.96 (sextet, 1H, J = 7.0 Hz), 4.67 (s, 1H), 5.13 (br, 1H), 6.59 (br, 1H), 6.72 (d, 1H, J = 8.0 Hz), 7.03 (d, 1H, J = 8.0 Hz). ^{13}C NMR: 17.7, 20.8, 21.1, 25.7, 26.1, 31.4, 37.3, 116.2, 121.7, 124.6, 126.8, 130.0, 132.0, 136.5, 152.8. MS (EI): 218, 203, 161, 148, 138, 119, 91, 77. HRMS: calcd. for $C_{15}H_{22}O$, 218.1751, found 218.1743. Compound **4**, IR (neat): 1070, 1420, 1254, 1619, 1711, 2859, 2924 cm^{-1}. ^1H NMR: 1.12–1.70 (m, 15H), 2.05 (br, 1H), 2.23 (s, 3H), 3.15–3.18 (m, 1H), 5.02 (br, 1H), 6.61 (s, 1H), 6.78 (d, 1H, J = 7.8 Hz), 7.01 (d, 1H, J = 7.8 Hz). ^{13}C NMR: 21.16, 22.23, 28.99, 29.61, 31.47, 37.96, 43.75, 71.93, 116.60, 121.40, 126.97, 131.07, 136.40, 153.70. MS (EI): 236, 218, 203, 161, 148, 135, 121, 91. HRMS: calcd. for $C_{15}H_{24}O_2$, 236.1856, found 236.1853. Compound **9b**, ^1H NMR: 1.66 (s, 3H), 2.35 (s, 3H), 3.87 (s, 3H), 4.42 (s, 1H), 5.04, (dd, 1H, J = 10.8 Hz, J = 1.2 Hz), 5.14, (dd, 1H, J = 17.2 Hz, J = 1.2 Hz), 6.18, (dd, 1H, J = 17.6 Hz, J = 10.8 Hz), 6.751 (s, 1H), 6.77 (d, 1H, J = 8 Hz), 7.20 (d, 1H, J = 8 Hz), ^{13}C NMR: 22.3, 27.2, 55.4, 74.7, 111.3, 112.5, 121.4, 126.4, 130.8, 138.5, 145.0, 156.9. HRMS: calcd. for $C_{12}H_{16}O_2$, 192.1150, found 192.1151. Compound **9c**, 1.68 (s, 3H), 2.22 (s, 3H), 3.80 (s, 3H), 3.83 (s, 3H), 4.44 (s, 1H), 5.07 (dd, 1H, J = 10.8 Hz, J = 1.2 Hz), 5.16, (dd, 1H, J = 17.2 Hz, J = 1.2 Hz), 6.18, (dd, 1H, J = 17.2 Hz, J = 10.8 Hz), 6.75 (s, 1H), 6.84 (s, 1H). ^{13}C NMR: 16.0, 27.3, 56.0, 56.1, 74.7, 109.5, 111.5, 114.9, 126.2, 131.8, 144.9, 150.5, 151.6. HRMS: calcd. for $C_{13}H_{18}O_3$ 222.1256, found 222.1258.