

A SIMPLE AND FACILE TOTAL SYNTHESIS OF SESQUITERPENE,
CUPARENE BY USING FURAN DERIVATIVES

Tetsuji Kametani, Masayoshi Tsubuki, and Hideo Nemoto

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai
980, Japan

Abstracts — 5-Methyl-2-(4-methylbenzyl)furan (4) obtained from the condensation of 2-lithio-5-methylfuran with 4-methylbenzyl bromide was converted into 3-methyl-2-(4-methylbenzyl)cyclopent-2-one (6) via 1-(4-methylphenyl)-hexane-2,5-dione (5). 1,4-Addition of methyl group into 6 furnished 3,3-dimethyl-2-(4-methylphenyl)cyclopentanone (7). This result constitutes a formal total synthesis of cuparene (9).

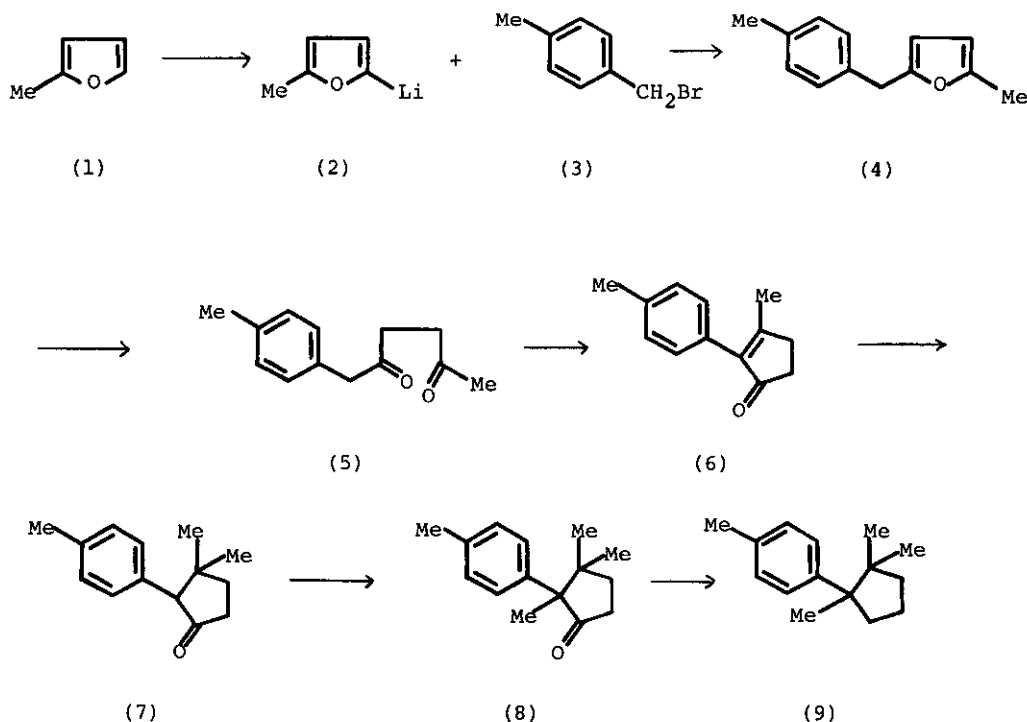
Since the first isolation of the sesquiterpene hydrocarbon cuparene (1) by Enzell and Erdtman¹, many related compounds with various oxidation patterns in the aromatic and alicyclic rings have been identified². Some of these compounds have been shown to have antifungal and antibiotic properties and a number of syntheses which directed towards cuparene itself or to simply related compounds have been reported³⁻⁹. We now wish to report a simple and efficient synthesis of cuparene (1) as a continuation^{10,11} of synthetic approaches to the terpenoid compounds by using furan derivatives.

Metalation¹² of 2-methylfuran (1) with n-butyllithium in an ethereal solution afforded 2-lithio-5-methylfuran (2) which on condensation with 4-methylbenzyl bromide¹³ yielded 5-methyl-2-(4-methylbenzyl)furan (4) in 72 % yield as a colourless oil, bp 110^o (6 mmHg) [nmr(CCl₄) δ 2.2 and 2.8 (3H, each s, 2 x ArCH₃), 3.78 (2H, s, CH₂), 5.7 (2H, s, ArH of furan ring), and 6.97 (4H, s, ArH of benzene ring); Mass m/e 186 (M⁺)]. Hydrolysis of 4 in aqueous acetic acid containing 20 % sulphuric acid furnished the diketone 5 as a pale yellow oil [ir(CHCl₃) 1710 cm⁻¹ (C=O); nmr(CCl₄) δ 2.0 and 2.3 (3H, each s, 2 x CH₃), 2.5 (4H, s, COCH₂CH₂CO), 3.53 (2H, s, ArCH₂CO), and 6.93 (4H, s, ArH); Mass m/e 204 (M⁺)] which was subjected to base-catalysed cyclization to

give the cyclopentenone **6** in 42 % yield (based on the furan **4**) as colourless plates, mp 108 ~ 109° [ir(CHCl₃), 1640 (C=C) and 1680 cm⁻¹ (CO); nmr (CCl₄) δ 2.15 (3H, s, ArCH₃), 2.35 (3H, s, CH₃), 2.2-2.7 (4H, m, 2 x CH₂), and 7.03 (4H, s, ArH); Mass m/e 186].

Secondly, the 1,4-addition of methyl group to the cyclopentenone system of compound **6** was effected by using lithium dimethylcuprate in the presence of dimethyl sulphide to afford the pentanone **7** in 65 % yield as colourless needles mp 81 ~ 82° [ir(CHCl₃), 1740 cm⁻¹ (CO); nmr(CCl₄) δ 0.67 and 1.11 (3H, each s, 2 x CH₃), 1.5-1.97 (2H, m, CH₂), 2.0-2.55 (2H, m, CH₂CO), 2.4 (3H, s, ArCH₃), 2.99 (1H, s, ArCH); Mass m/e 202 (M⁺)]. The compound **7** thus obtained has been converted to cuparene (**9**) via the compound **8** by de Mayo⁹ and this work constitutes a formal total synthesis of cuparene (**9**).

Scheme



Thus, we could demonstrate a simple synthesis of cuparene through furan intermediates which could be applied to the synthesis of the same type of sesquiterpenes.

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