HETEROCYCLES. Vol 12, No 6, 1979

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

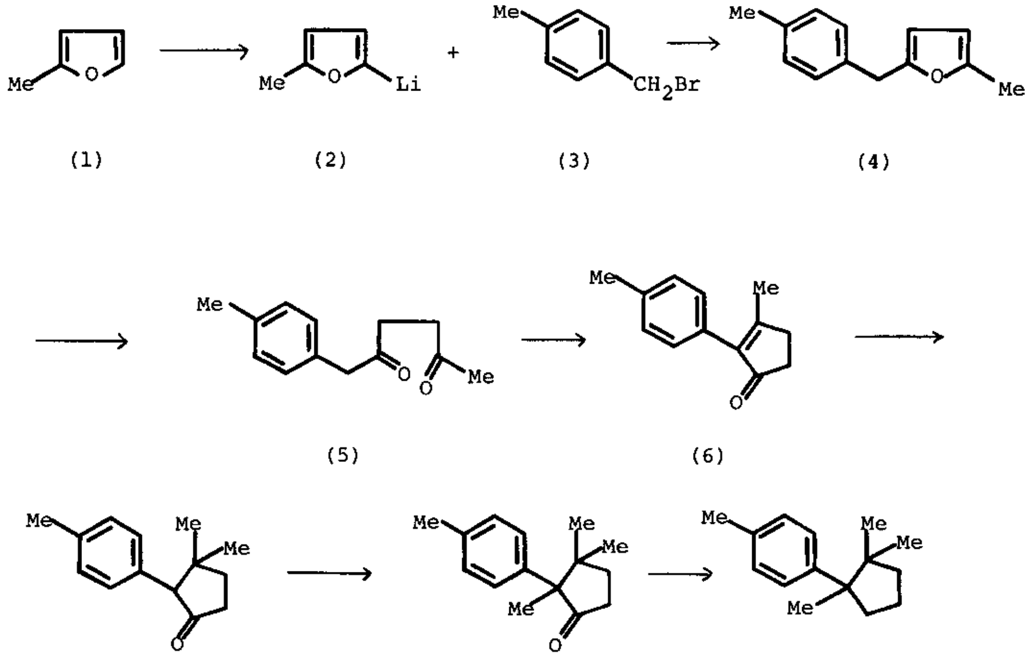
Abstracts —— 5-Methyl-2-(4-methylbenzyl)furan (**4**) obtained from the condensation of 2-lithio-5-methylfuran with 4-methylbenzyl bromide was converted into 3-methyl-2-(4-methylbenzyl)cyclopenten-2-one (**6**) via 1-(4-methylphenyl)-hexane-2,5-dione (**5**). 1,4-Addition of methyl group into **6** furnished 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 Erdtman[1], many related compounds with various oxidation patterns in the aromatic and alicyclic rings have been identified[2]. 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 reported[3-9]. 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.

Metalation[12] of 2-methylfuran (**1**) with n-butyllithium in an ethereal solution afforded 2-lithio-5-methylfuran (**2**) which on condensation with 4-methylbenzyl bromide[13] yielded 5-methyl-2-(4-methylbenzyl)furan (**4**) in 72 % yield as a colourless oil, bp 110° (6 mmHg) [nmr(CCl_4) δ 2.2 and 2.8 (3H, each s, 2 x Ar$C\underline{H}_3$), 3.78 (2H, s, CH_2), 5.7 (2H, s, Ar$\underline{H}$ of fruan ring), and 6.97 (4H, s, Ar$\underline{H}$ 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($CHCl_3$) 1710 cm^{-1} (C=O); nmr(CCl_4) δ 2.0 and 2.3 (3H, each s, 2 x CH_3), 2.5 (4H, s, $COCH_2CH_2CO$), 3.53 (2H, s, Ar$C\underline{H}_2$CO), and 6.93 (4H, s, Ar$\underline{H}$); 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($CHCl_3$), 1640 (C=C) and 1680 cm^{-1} (CO); nmr (CCl_4) δ 2.15 (3H, s, $ArC\underline{H}_3$), 2.35 (3H, s, CH_3), 2.2-2.7 (4H, m, 2 x CH_2), and 7.03 (4H, s, $Ar\underline{H}$); 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[9] in 65 % yield as colourless needles mp 81 ∿ 82° [ir($CHCl_3$), 1740 cm^{-1} (CO); nmr(CCl_4) δ 0.67 and 1.11 (3H, each s, 2 x CH_3), 1.5-1.97 (2H, m, CH_2), 2.0-2.55 (2H, m, CH_2CO), 2.4 (3H, s, $ArC\underline{H}_3$), 2.99 (1H, s, $ArC\underline{H}$); Mass m/e 202 (M^+)]. The compound 7 thus obtained has been converted to cuparene (9) <u>via</u> the cpmpound 8 by de Mayo[9] 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.

REFERENCES

1. C. Enzell and H. Erdtman, Tetrahedron, 1958, 4, 361.
2. T. K. Devon and A. I. Scott, "Handbook of Naturally Occurring Compounds, Vol. II. Terpenes", Academic Press, 1972.
3. W. Parker, R. Ramage, and R. A. Raphael, J. Chem. Soc., 1962, 1558.
4. P. T. Lansbury and F. R. Hilfiker, Chem. Comm., 1969, 619; P. T. Lansbury, E. J. Nienhouse, D. J. Scharf, and F. R. Hilfiker, J. Amer. Chem. Soc. , 1970, 92, 5649.
5. P. Leriverend, Bull. Soc. chim. France, 1973, 3498.
6. O. P. Vig, R. K. Parti, K. C. Gupta, and M. S. Bhatia, Indian J. Chem., 1973, 11, 981.
7. R. B. Mane and G. S. K. Rao, J. C. S. Perkin I, 1973, 1806.
8. C. W. Bird and Y. C. Yeong, Synthesis, 1974, 27.
9. P. de Mayo and R. Suan, J. C. S. Perkin I, 1974, 2559.
10. T. Kametani, H. Nemoto, and K. Fukumoto, Heterocycles, 1974, 2, 639.
11. T. Kametani, H. Nemoto, M. Takeuchi, S. Hibino, and K. Fukumoto, Chem. and Pharm. Bull. (Japan), 1976, 24, 1354.
12. G. Büchi and H. Wüest, J. Org. Chem., 1966, 31, 977.
13. G. Kubiczek and L. Neugebauer, Monatsh., 1950, 81, 917.

Received, 6th April, 1979