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A NEW SYNTHETIC METHOD FOR THE KEY INTERMEDIATE OF THE EUDESMANE CLASS OF SESQUITERPENES THROUGH FURAN DERIVATIVES

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A versatile synthetic method for the key intermediate (VIII), which has properly protected carbonyl functions at both the C - 1 and C - 5 positions, for the synthesis of the eudesmane sesquiterpenes, is described.

The eudesmane class of sesquiterpenes has received a considerable synthetic attention.[1] Although a few syntheses of eudesmane-type sesquiterpenes through Birch reduction of tetralin derivatives have been reported,[2] many synthetic approaches have utilized the Robinson annelation sequence to construct the bicyclic skeleton characteristic of this group of natural products. As part of our own synthetic studies, we have developed a new synthetic method of a key intermediate (VIII) which has properly protected carbonyl functions at both C - 1 and C - 5 for the synthesis of the eudesmane sesquiterpenes starting from 2-methylfuran.

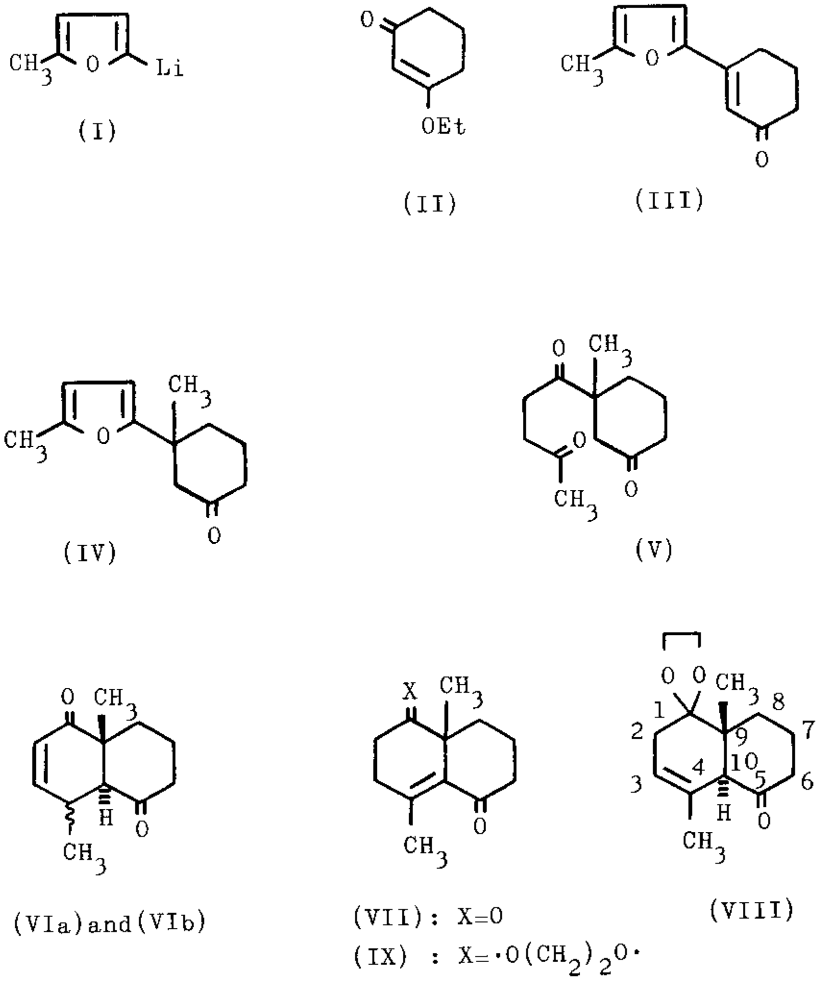
Metalation of 2-methylfuran with n-butyllithium in ethereal solution yielded 2-lithio-5-methylfuran (1)[3] which on reaction with 3-ethoxy-2-cyclohexenone (II) followed by treatment with 10 % sulphuric acid gave 3-(5-methylfuryl)-2-cyclohexenone (III), m.p. 79° ν (CHCl$_3$) 1640 and 1600 cm^{-1}; δ (CDCl$_3$) 2.34 (s, 3H), 6.08 (d, 1H, *J* 3.0 Hz), 6.35 (s, 1H), 6.61 (d, 1H, *J* 3.0 Hz), in 51 % yield. An ethereal solution of (III) was added to a mixture of methyl copper and tri-n-butylphosphine in ether[4] at - 30°, and the resulting mixture was stirred for 1 hr at - 30°, then 3 hr at room temperature to give the methylated furano-ketone (IV), bp$_3$ 80° ν (CHCl$_3$) 1695 cm^{-1}; δ (CDCl$_3$) 1.30 (s, 3H), 2.24 (s, 3H), 5.83 br (s, 2H), in 62 % yield.

The furan ring of compound (IV) was surprisingly easy to be hydrolysed with concentrated hydrochloric acid in methanol at room temperature to give the triketone (V), bp$_3$ 140°, ν (CDCl$_3$) 1700 cm^{-1}; δ (CDCl$_3$) 1.26 (s, 3H), 2.14 (s, 3H), in quantitative yield. Then we attempted an acid-catalyzed cyclization of the triketone (V) by refluxing a solution of (V) in concentrated hydrochloric acid in methanol overnight. The crude product was subjected to chromatography to give three compounds. Compound (VIa) was obtained from the first fraction as colourless prisms, m.p. 92°, ν (CHCl$_3$) 1670 and 1701 cm^{-1}; δ (CDCl$_3$) 1.00 (s, 3H), 1.11 (d, 3H, *J* 7 Hz), 5.79 (q, 1H, *J* 3 and 10 Hz), 6.58 (q, 1H, *J* 3 and 10 Hz); *m/e* 192 (M$^+$), in 26 % yield. From the second fraction, compound (VIb), ν (CHCl$_3$) 1675 and 1705 cm^{-1}; δ (CDCl$_3$) 1.13 (s, 3H), 1.10 (d, 3H, *J* 7 Hz), 5.88 (q, 1H, *J* 3 and 10 H), 6.65 (q, 1H, *J* 3 and 10 Hz); *m/e* 192 (M$^+$), was obtained in 25 % yield. Compound (VII), ν (CHCl$_3$) 1670 and 1705 cm^{-1}; δ (CDCl$_3$) 1.19 (s, 3H), 1.88 (s, 3H); *m/e* 192 (*M*$^+$), was obtained from the third fraction in 9 % yield.

A benzene solution of 1 : 1 mixture of compounds (VIa) and (VIb), ethylene glycol and a catalytic amount of toluene-p-sulphonic acid was refluxed for 12 hr under removing water which generated during the reaction, giving a single compound (VIII), after purification by chromatography, m.p. 87°, ν ($CHCl_3$) 1705 cm^{-1}; δ ($CDCl_3$) 1.08 (s, 3H), 1.90 (m, 3H), 2.75 br (s, 2H), 3.80 (s, 4H), 5.53 br (s, 1H), m/e 236 (M^+), in 55 % yield. The presence of coupling among C - 2 protons, C - 3 vinylic proton and C - 4 vinyl methyl protons was confirmed by double irradiation studies of each signal. Compound (VIII) was treated with sodium methoxide in methanol overnight at room temperature in order to examine the stability of compound (VIII) which was recovered unchanged. From the above experiment the octalone ring system of compounds (VIa, VIb, and VIII) was assigned to be trans-fusion tentatively. It was also found that compound (VIII) is more stable than compound (IX) by basic treatment of compound (VIII) as described above.

Thus, the first example of the synthesis of key intermediate for the eudesmane class of sesquiterpenes through furan derivatives, in surprisingly high yield, including transformation of furan derivative (IV) to triketone (V) was accomplished.

Scheme


CH3
O
Li
(I)
O
OEt
(II)
CH3
O
O
(III)
CH3
CH3
O
O
(IV)
O
CH3
O
CH3
O
(V)
O
CH3
H
CH3
O
(VIa) and (VIb)
X
CH3
CH3
O
(VII) : X=O
(IX) : X=·O(CH2)2O·
O O
CH3
1
2
3
4
5
6
7
8
9
10
H
CH3
O
(VIII)

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3 Cf. V. Ramanathan and R. Levine, *J. Org. Chem.*, 1962, **27**, 1216.

4 Cf. Recent review on organo-copper compounds, J. F. Normant, *Synthesis*, 1972, 63.

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