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An Efficient Synthesis of the Natural (+)-Fulvanin 1

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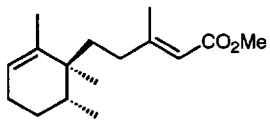
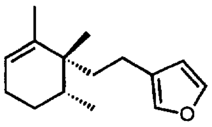
Abstract: *Pulegone was used for the first total synthesis of (+)-fulvanin 1 adopting chiron approach. Pertinent methodology includes stereocontrolled Michael-type reaction, functional group adjustements and Wittig olefination.*

In connection with studies directed toward methodologies for the total synthesis of sesquiterpenoids,[1,2] a new method for a highly stereoselective introduction of the side chain and consequently an efficient purification of the desired diastereoisomer was required. We have reported that the alkylation of 2,3-dimethylcyclohexanone with a functionalized allylic bromide provided a stereoselective incorporation of the side chain.[3] This method required several steps for functional group transformations to accomplish the first synthesis of racemic form of fulvanin 1. It appeared to us that with an efficient stereoselective formation of the methyl groups in a *cis* relationship involving an easier side chain transformation, we would achieve the total synthesis of the natural enantiomer (+)-fulvanin 1. Thus, it became imperative to explore various routes for the desired *S,E*-stereochemistry of the side chain. The absolute stereochemistry of (+)-fulvanin 1 has been proposed[4,5] as *5R,6S* in contradiction with the *5R,6R* configuration deduced for (-)-microcionin 2.[6]

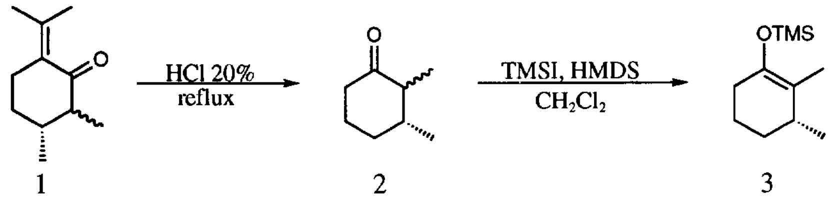


(+)-fulvanin 1



(-)-microcionin 2

In considering an appropriate synthetic scheme, it at first seemed reasonable to start with a monoterpene of known absolute stereochemistry. (*R*)-(+)-Pulegone, an inexpensive compound, was transformed to methylpulegone (**1**) using the standard procedures and then converted by retro-aldolisation into (*3R*)-2,3-dimethylcyclohexanone[7] (**2**) (*Scheme 1*). Compound **2** was used as silyl enol ether **3** in a Michael-type reaction .



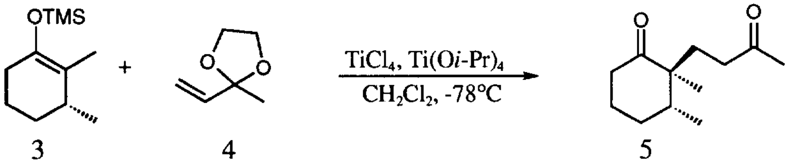
Scheme 1

The Michael addition is a synthetic procedure of great value.[8,9] However, it has been recognized that in presence of basic catalysts it was beset with serious problems which limit its utility[10]. In those conditions, methyl vinyl ketone used as a Michael acceptor tend to polymerize[11] and with the reversible nature of the initial Michael reaction it is not usually possible to employ thermodynamically generated enolates.[10c]

A variable alternative to the conventional Michael reaction conditions is the Lewis acid-catalized addition of silyl enol ethers.[12] Many Lewis acids have been tried and important observations were made concerning the stereoselection of these additions. The formation of the anti diastereoisomer as a major product appears to be general.[13]

The alkylation of methyl vinyl ketone with the thermodynamically generated silyl enol ether of (*3R*)-2,3-dimethylcyclohexanone (**2**) with Lewis acid appeared to be a very attractive chiron approach[14] for the introduction of the side chain of (+)-fulvanin 1. The starting (*3R*)-2,3-dimethyl-1-trimethylsiloxycyclohex-1-ene (**3**) was prepared by following the previously reported procedure[15] leading predominantly to the thermodynamically favoured isomer (87:13).

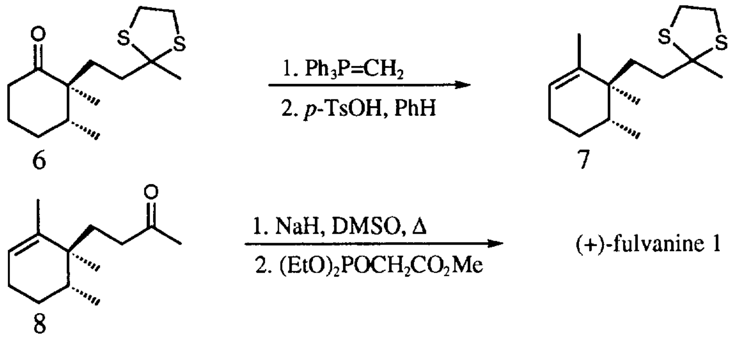
We first examined conjugated addition of the silyl enol ether **3** to methyl vinyl ketone using BF_3 etherate as catalyst in the presence of one equivalent of dibenzoyltartaric acid.[12a] As was expected, the stereocontroled introduction of the 3-oxobutyl chain was effective leading predominently to the desired *2S,3R* structure of the diastereoisomeric 1,5-diketone **5**. However, it was of interest to find a more useful experimental procedure. We therefore examined other Lewis acids as catalysts and finally chose the $TiCl_4$, Ti(O*i*-Pr)$_4$ (1:1) method,[12c] using 1-buten-3-one ethylene ketal (**4**) as Michael acceptor (*Scheme 2*).



Scheme 2

The isomeric 1,5-diketones were transformed into corresponding dithiolanes derivatives[16] (**6**), providing an easier purification of diastereoisomers by flash chromatography.[17] The protection of methylketone can also be accomplished *in situ* after the conjugate addition.

Conversion of compound **6** into methylcyclohexene **7** has been done by the addition of either methyllithium or methylmagnesium bromide, followed by dehydration or Wittig olefination[18] and subsequent double bond isomerisation (*Scheme 3*). Cleavage of the dithiolane[19] group of compound **7** was best effected using $Hg(ClO_4)_2$ in aqueous THF at room temperature for 20 minutes giving methyl ketone **8**.[20] Finally, a Horner-Emmons reaction[21] efficiently transformed coumpound **8** into the corresponding α,β-unsaturated esters in an *E*:*Z* proportion of 73:27 (*Scheme 3*). The desired *E* stereoisomer was easely separated leading to the targeted (+)-fulvanin 1, which proved to be spectroscopically identical to the naturally occurring product[22] except for the optical rotation: $[\alpha]^{22}_D = +20.8$ (c = 0.4, $CHCl_3$).[23] Natural (+)-fulvanin 1 exhibits $[\alpha]_D = +7.9$ (c = 0.4, $CHCl_3$)[4] and $[\alpha]^{24}_D = +12.2$ (c = 1.01, $CHCl_3$).[5]



Scheme 3

The viability of the Michael-type approach to the (2*S*,3*R*)-2-subtituted-2,3-dimethylcyclohexanones has been demonstrated by an asymmetric total synthesis of (+)-fulvanin 1. The intermediate (+)-1,5-diketone (**5**) can be used for preparation of other bicyclic sesquiterpenes (e.g.: (-)-ishwarane and (-)-aristolone). These natural products present the same structure system. By controlling first the absolute and then the relative stereochemistry of the two adjacent tertiary and quaternary carbon centers, the 1,5-diketone **5** can be transformed into the corresponding decalone.

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17- The stereochemistry of the pure isomeric **6** is evident from his NMR spectrums. IR (film): 2920, 1700, 1440, 1370, 1310, 1270, 1240, 1220, 1135, 1110, 1045, 1030, 970, 940, 840, 745, 680 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 0.90 (d, J = 6.8 Hz, 3H), 0.98 (s, 3H), 1.52-1.96 (m, 9H), 1.75 (s, 3H), 2.35 (t, J = 6,7 Hz, 2H), 3.30 (m, 4H). ^{13}C NMR (300 MHz, $CDCl_3$): 15.33, 18.95, 23.82, 28.59, 32.10, 33.53, 38.22, 38.49, 39.48, 39.60, 39.67, 51.74, 66.85, 215.48. $[\alpha]^{34}_{D} = -13$ (c = 0.27, $CHCl_3$).

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20- IR (film): 3005, 2810, 1710, 1430, 1350, 1270, 1220, 1150, 1070, 1035, 1015, 1000, 985, 910, 845, 790, 720, 620. ^{1}H NMR (300 MHz, $CDCl_3$): 0.83 (d, J = 6,6 Hz, 3H), 0.86 (s, 3H), 1.37-1.71 (m, 5H), 1.54 (bs, 3H), 1.89-1.93 (m, 2H), 2.12 (s, 3H), 2.05-2.18 (m, 1H), 2.30-2.42 (m, 1H), 5.43 (m, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): 15.76, 18.87, 20.58, 25.43, 26.86, 29.41, 29.88, 33.57, 38.85, 39.97, 124.79, 138.73, 209.17. $[\alpha]^{22}_{D} = +38.8$ (c = 2.0, $CHCl_3$).

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22- IR (film): 3005, 2910, 1715, 1640, 1425, 1370, 1350, 1270, 1215, 1140, 1070, 1020, 1000, 910, 860, 840, 795, 730. ^{1}H NMR (300 MHz, $CDCl_3$): 0.84 (d, J = 6.2 Hz, 3H), 0.85 (s, 3H), 1.32-2.14 (m, 9H), 1.58 (bs, 3H), 2.14 (bs, 3H), 3.66 (s, 3H) 5.42 (m, 1H), 5.65 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): 15.65, 18.95, 20.82, 25.36, 26.84, 27.35, 33.19, 34.31, 35.61, 40.32, 50.61, 114.52, 124.55, 138.83, 161.39, 167.16.

23- A higher specific rotation for synthetic terpenoids has previously been reported. For example: Hansson, T.; Wickberg,B.; *J. Org. Chem.* **1992**, *57*, 5370.

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