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# The First Enantioselective Synthesis of (-)-Microcionin 2

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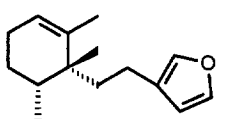
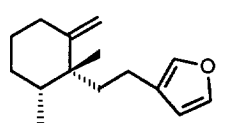
**Key Words** : Rieke ® magnesium, 2-(3-furyl)ethyl bromide; (R)-(+)-4-methylcyclohex-2-en-1-one; (-)-microcionin 2.

***Abstract:*** *An approach known to give regiospecific and stereospecific reactions has been applied to the enantioselective synthesis of the natural (-)-microcionin 2 (**1**), a prototype of trans relationship of the methyl groups on the furanosesquiterpenes.* Copyright © 1996 Elsevier Science Ltd

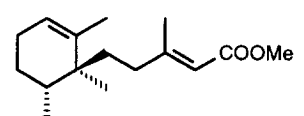
Although both *cis* and *trans* adjacent dimethyl configurations are known in the case of naturally occurring monocyclosesquiterpenes, characterized by a rearranged cyclofarnesane skeleton, only the *trans* modification seems to has been attributed to the microcionin 2 (**1**) and microcionin 4 (**2**). Two independent groups reported the isolation and characterization of these natural compounds. First, the microcionins have been isolated, from the sponge *Microciona toxystila*,[1] and later from the dorid nudibranch molluscs *Dendrodoris grandiflora*, growing in contact with them[2]. The second group has also isolated these furanosesquiterpenes, from another specimen of dorid nudibranch molluscs, *Cadlina luteomarginata*[3]. The proposed structure of microcionins was established from spectroscopic data and chemical transformations of **1**[1]. On the basis of comparison with (+)-fulvanin 1 (**3**)[4], characterized by a *cis* relationship of the methyl groups, the NMR spectral data showed differences between this compound and microcionins.




**1**




**2**




**3**

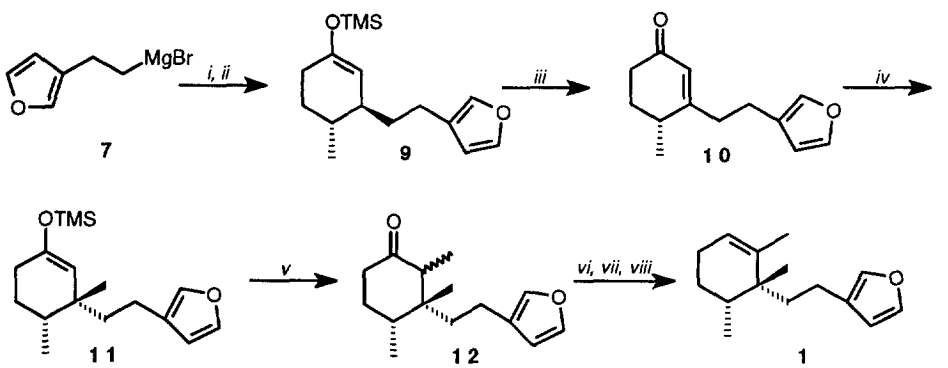
As part of our program to extend the use of organometallic compounds in the total synthesis of sesquiterpenoids, we considered the enantioselective total synthesis of (-)-microcionin 2 (**1**), and confirm the absolute configuration of this type of furanosesquiterpene. In addition, it was recently proposed a *cis* configuration of the two methyl groups, for two new isolated furanoditerpenes from *Acalypha* species[5].

In this paper, we wish to report the first enantioselective total synthesis of the enantiomerically pure (-)-microcionin 2 (**1**). The stereocontrolled incorporation of the side chain and subsequently, the construction of

the adjacent quaternary new chiral center, has been achieved by cuprous-mediated conjugate addition of Grignard reagent **7**, prepared from 2-(3-furyl)ethyl bromide (**6**), to (R)-(+)-4-methylcyclohex-2-en-1-one (**8**). Preparation of this labile dextrorotatory cyclenone **8**[6-8], was advantageously effected by an important modification relatively in the direct introduction of the 2,3-insaturation, without any protection of the carbonyl group of the acyloin prepared from (R)-(+)-pulegone[9].

A high yield route to 2-(3-furyl)ethyl bromide (**6**) used for the preparation of the Grignard reagent **7**[10], is provided with modifications of the more recent method[11]. For example, while this method is caracterized by a lack of regioselectivity, leading to a mixture of 3-methyl-2-furonitrile and 3-furylacetonitrile (**5**), our method of 3-furylmethyl chloride (**4**) with sodium cyanide in dimethylsulfoxide gave in quantitative yield, the 3-furylacetonitrile (**5**). Thus, basic hydrolysis produced the corresponding carboxylic acid, in high yield, which by reduction without purification, afforded the 2-(3-furyl)ethanol. Bromination using carbon tetrabromide and triphenylphosphine, afforded the bromide **6** with a yield of 76%.

Optimization was required for the preparation of the corresponding Grignard reagent **7**[12] since this is one of the reagent of choice for copper-mediated conjugate additions. The conventional method of generating **7** using magnesium turnings invariably gave low yield. We thus choose the commercial Rieke® magnesium powder in THF solution[13]. The reaction was performed carefully in the same solvent, in order to increase the reaction yield, and consequently, to decrease the formation of Wurtz coupling byproduct. The obtained organomagnesium compound **7** *(Scheme 1)* gave improved results of conjugate addition to the (R)-(+)-4-methylcyclohex-2-en-1-one (**8**), using cuprous iodide, in the presence of triethylamine and trimethylsilyl chloride, which increase yield and the rate of reaction.




*i:* CuI, -10°C; *ii:* **8**, TMSCl, $Et_3N$,-40°C, 56%; *iii:* $Pd(OAc)_2$, MeCN, 3 h, 60%; *iv:* MeLi, CuI, TMSCl, $Et_3N$, THF, -78°C, 84%; *v:* MeLi, 0°C, MeI, -22 to 25°C, 40%; *vi:* $NaBH_4$, MeOH, 95%; *vii:* MsCl, Pyr.,$CH_2Cl_2$, 90%; *viii:* DMSO, 50°C, 24 h, 98%.

**Scheme 1**

The regioselectively generated chiral silyl enol ether **9** was subjected to the oxidation under stoichiometric palladium (II) acetate method, previously reported[14] for the synthesis of (4R)-(+)-3,4-dimethyl-

cyclohex-2-en-1-one, affording the key intermediate (4R)-(+)-3-[2-(3-furyl)ethyl]-4-methylcyclohex-2-en-1-one **(10)**[15]. Experimentally, several precautions should be observed: the chemical and optical yields of **10** were reduced upon prolonged reaction times, and use of excess palladium (II) acetate. Also, the product must be purified in a reasonably short period of time in order to avoid any epimerization. Consequently, for the construction of the new chiral quaternary center, bearing the required R configuration, the freshly purified enone **10** was immediatly used in the subsequent dimethylcuprate 1,4-addition producing the silyl enol ether **11**.

A carefully executed α methylation of **11** with methyllithium generated a site-specific enolate quenched by the action of methyl iodide, completed the preparation of the (3R,4R)-3-[2-(3-furyl)ethyl]-2,3,4-trimethylcyclohexanone **(12)**[16] as a major regioisomer. The sodium borohydride reduction of tetrasubstituted cyclohexanone **12** gave the secondary alcohol in 95 % yield, which was treated with methanesulfonyl chloride in pyridine for 12 h at 0°C in order to accomplish an efficient elimination. In this process, the quantitatively resulting mesylate was heated at 50°C in dimethylsulfoxide for a day, and the regioselective elimination produced only the naturally occurred levorotatory microcionin 2 **(1)**[17].

The present study clearly demonstrates that the key intermediate chiral (4R)-(+)-3-[2-(3-furyl)ethyl]-4-methylcyclohex-2-en-1-one **(10)** may be readily prepared without epimerization. By controlling the absolute configuration of the two adjacent carbon centers, the preparation of trisubstituted silyl enol ether **11** was efficiently accomplished. The regiocontrolled alkylation yielded the desired tetrasubstituted cyclohexanone **12**, precursor of furanosesquiterpenoids characterized by *trans* relationship of the two methyl groups. The viability of this approach to prepare the rearranged cyclofarnesane structure has been demonstrated by a first total synthesis of the natural (-)-microcionin 2.

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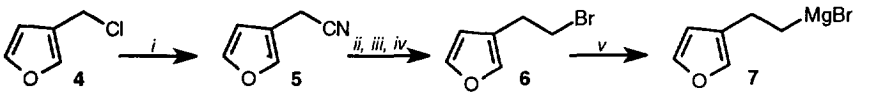
9. The reduction of (R)-(+)-pulegone with LAH (94%, oil), followed by ozonolysis in $CH_2Cl_2$, afforded only one diastereomeric acyloin (78%, oil), upon treatment with excess of MsCl (5 eq) and pyridine, in $CH_2Cl_2$, (at 0°C for 6 h, and then at rt for 12 h), afforded the mesylate (84%, solid). Bromination

with LiBr in acetone at rt (57%, oil), followed by elimination with $Li_2CO_3$ in refluxing DMF (1.5 h.), gave (R)-(+)-4-methylcyclohex-2-en-1-one (**8**) (90%, oil, $[\alpha]_D$ = +110 (c = 3.5, $CHCl_3$); Lit [8] $[\alpha]_D$ = +113 (c = 1.41, $CHCl_3$)).

10.




*i:* NaCN, DMSO, 97%; *ii:* KOH 20%, MeOH, Δ, 80%; *iii:* LAH, $Et_2O$, 97%; *iv:* $CBr_4$, $PPh_3$, $CH_2Cl_2$,76% *v:* Mg Rieke, THF.


11. Tanis, S.P. and Herrinton, P.M. *J. Org. Chem.* **1985**, *50*, 3988.
12. The formation of the Grignard reagent **7** is highly dependant on solvent and on the type of magnesium.
13. Solution of 2.5 g of Rieke® Magnesium in 50 mL of THF. Rieke Metals Inc., 6133 Heide Lane, Lincoln, Nebraska 68512, Tel & Fax (402) 472-9044.
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15. Data for (4R)-(+)-3-[2-(3-furyl)ethyl]-4-methylcyclohex-2-en-1-one (**10**) are as follows : $^1$H NMR (300 MHz; $CDCl_3$): δ 7.28 (bs, 1H), 7.16 (bs, 1H), 6.20 (bs, 1H), 5.77 (s, 1H), 2.58 (m, 2H), 2.41 (m, 4H), 2.28 (m, 1H), 2.05 (m, 1H), 1.75 (m, 1H), 1.14 (d, 3H, J=7,0 Hz); $^{13}$C NMR (75 MHz; $CDCl_3$): δ 199.4, 168.8, 142.9, 138.8, 125.1, 123.6, 110.5, 35.7, 34.0, 33.0, 30.0, 22.4, 17.6. IR (neat) 2920, 1670, 1615, 1440, 1250, 1195, 1160, 1020, 870, 770, 725 $cm^{-1}$. $[\alpha]_D$ = +53.1 (c = 0.67, $CHCl_3$); Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.55; H, 8.29.
16. Data for (3R,4R)-3-[2-(3-furyl)ethyl]-2,3,4-trimethylcyclohexanone (**12**) are as follows : $^1$H NMR (300 MHz; $CDCl_3$): δ 7.34 (bs, 1H), 7.21 (bs, 1H), 6.26 (bs, 1H), 2.50 (q, 1H, J=6.9 Hz), 2.36 (m, 4H), 1.95 (m, 2H), 1.72-1.42 (m, 3H), 1.11 (d, 3H, J=7.0 Hz), 1.00 (d, 3H, J=6.9 Hz), 0.89 (s, 3H); $^{13}$C NMR (75 MHz; $CDCl_3$): δ 215.1, 142.7, 138.4, 126.1, 110.8, 50.0, 43.4, 37.0, 36.8, 34.4, 29.4, 21.1, 18.5, 14.1, 9.2.
17. Data for (-)-microcionin 2 (**1**) are as follows : $^1$H NMR (300 MHz; $CDCl_3$): δ 7.33 (bs, 1H), 7.20 (bs,1H), 6.26 (bs, 1H), 5.43 (m, 1H), 2.32 (m, 2H), 1.97 (m, 2H), 1.68-1.41 (m, 5H), 1.64 (d, 3H, J=1.5 Hz), 1.07 (s, 3H), 0.97 (d, 3H, J=6.7 Hz).$^{13}$C NMR (75 MHz; $CDCl_3$: δ 142.49, 138.98, 138.22, 125.99, 122.83, 110.80, 39.50, 37.53, 36.11, 27.35, 26.15, 23.86, 20.80, 19.50, 15.85. $[\alpha]_D$ = - 51.4 (c = 0.54, $CHCl_3$); Lit [1] $[\alpha]_D$ = - 58.3 (the solvent and the concentration have not been specified). The chemical shifts of the methyl signals at C-3 and C-4 (δ 0.97 and 1.07), clearly demonstrated the proposed stereochemistry of (-)-microcionin 2 in comparison with (+)-fulvanin 1 (δ 0.86 and 0.87) lit [4].


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