



The First Enantioselective Synthesis of (-)-Microcionin 2

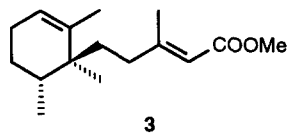
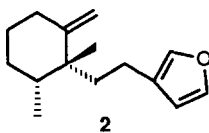
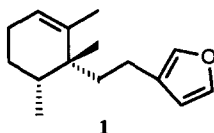
Steeves Potvin and Perséphone Canonne*

Département de chimie, Université Laval, Québec, Québec, Canada, G1K 7P4

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 have 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 them². 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.



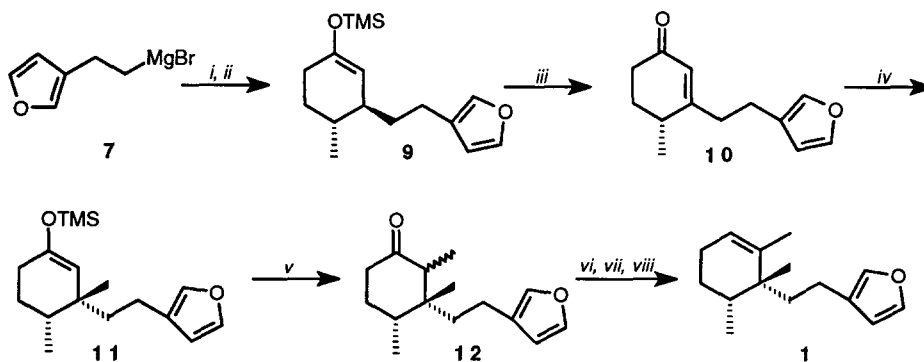
As part of our program to extend the use of organometallic compounds in the total synthesis of sesquiterpenoids, we considered the enantioselective total synthesis of (-)-microcionin 2 (**1**), and confirm the absolute configuration of this type of furanosesquiterpene. In addition, it was recently proposed a *cis* configuration of the two methyl groups, for two new isolated furanoditerpenes from *Acalypha* species⁵.

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)-(+)-pulegone⁹.

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 method¹¹. For example, while this method is characterized 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 solution¹³. 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, Et₃N, -40°C, 56%; *iii*: Pd(OAc)₂, MeCN, 3 h, 60%; *iv*: MeLi, CuI, TMSCl, Et₃N, THF, -78°C, 84%; *v*: MeLi, 0°C, MeI, -22 to 25°C, 40%; *vi*: NaBH₄, MeOH, 95%; *vii*: MsCl, Pyr., CH₂Cl₂, 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 reported¹⁴ 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 immediately used in the subsequent dimethylcuprate 1,4-addition producing the silyl enol ether **11**.

A carefully executed α methylation of **11** with methyl lithium 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.

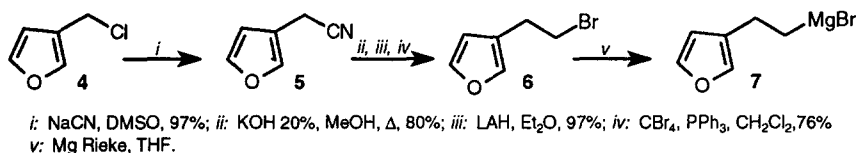
Acknowledgment: We gratefully acknowledge the Natural Sciences and Engineering Research Council of Canada for financial support of this work.

References and Notes

1. Cimino, G.; De Stefano, S.; Guerriero, A. and Minale, L. *Tetrahedron Lett.* **1975**, *43*, 3723.
2. Cimino, G.; De Rosa, S.; De Stefano, S.; Morrone, R and Sodano, G. *Tetrahedron* **1985**, *41*, 1093.
3. Hellou, J.; Andersen, R.J. and Thompson, J.E. *Tetrahedron* **1982**, *38*, 1875.
4. Angers, P. and Canonne, P. *Tetrahedron Lett.* **1995**, *36*, 2397.
5. Siems, K.; Jakupovic, J; Castro, V. and Poveda, L. *Phytochemistry* **1996**, *41*, 851.
6. Barieux, J.-J. and Gore, J. *Bull. Soc. chim. Fr.* **1971**, 3978.
7. Silvestri, M.G. *J. Org. Chem.* **1983**, *48*, 2419.
8. Lee, H.W.; Ji, S.K.; Lee, I.-Y.C. and Lee, J.H. *J. Org. Chem* **1996**, *61*, 2542.
9. The reduction of (R)-(+)-pulegone with LAH (94%, oil), followed by ozonolysis in CH₂Cl₂, afforded only one diastereomeric acyloin (78%, oil), upon treatment with excess of MsCl (5 eq) and pyridine, in CH₂Cl₂, (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.



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.
14. Danilshesky, S.; Chackalamannil, S.; Harrison, P.; Silvestri, M.G. and Cole, P. *J. Am. Chem. Soc.* **1985**, *107*, 2474.
15. Data for (4R)-(+)-3-[2-(3-furyl)ethyl]-4-methylcyclohex-2-en-1-one (**10**) are as follows : ^1H 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 $\text{C}_{13}\text{H}_{16}\text{O}_2$: 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 : ^1H 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 : ^1H 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.

(Received in USA 27 August 1996)