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TETRAHEDRON: *ASYMMETRY*

An easy approach to chiral non-racemic 6-(furan-3-yl)-5,6-dihydro-pyran-2-ones

Annunziata Soriente, Margherita De Rosa, Patrizia Dovinola, Guido Sodano and Arrigo Scettri *

Dipartimento di Chimica, Università di Salerno, 84081 Baronissi (SA), Italy

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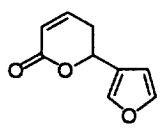
Abstract

Chiral non-racemic 6-(furan-3-yl)-pyran-2-one derivatives, key-intermediates in the preparation of compactin, manoalide and cacospongionolide subunits, are easily accessible through a rapid and convenient six-step sequence.

The strictly related subunits **1** and **2a,b** represent the main structural features of some natural products characterized by important biological activities, such as richardianidins[1] (as regards **1**), isolated from the leaves of the toxic plant *Cluytia richardiana*, manoalide[2] and cacospongionolide[3] (as regards **2a** and **2b** respectively) two naturally occurring antiinflammatory marine compounds, containing a pyranofuranone moiety which is considered to be the pharmacophoric group.



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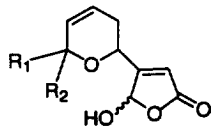

2 **a:** R_1 = OH R_2 = H
b: R_1 = R_2 = H

From a chemical point of view, the easy manipulation of the furan and of the pyranone rings allows the ready conversion of the substructure **1** into **2**.[4] Therefore, the preparation of compound **1** in both enantiomeric forms represents a main target of our research, devoted to the development of new synthetic sequences leading to chiral manoalide and cacospongionolide analogs.[5] Now we wish to report a new synthesis of chiral 6-(furan-3-yl)-5,6-dihydro-pyran-2-one (+)-**1** and (−)-**1** through a six-step sequence, whose efficiency and convenience can be mainly attributed to the employment of microwave (MW) irradiation for the achievement of highly selective processes (Scheme 1).

The first step involved the generation of the C-5 stereogenic centre by enantioselective aldol condensation of masked acetoacetic ester **4** in the presence of titanium tetraisopropoxide, as a transition

* Corresponding author. E-mail: titti@ponza.dia.unisa.it

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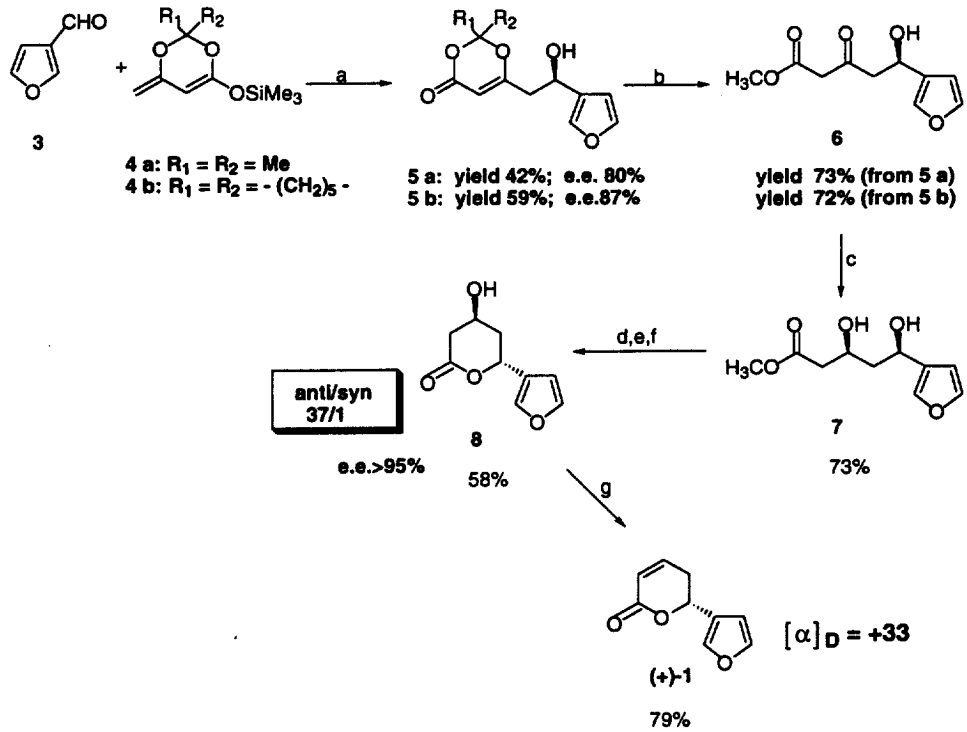


a= $Ti(OiPr)_4$/(R)-(-)-binaphthol; b= toluene, MeOH (12 equiv.), MW (P=250 W), 15 min.; c= Et_2BOMe, $NaBH_4$; d= NaOH/EtOH; e= H_2SO_4 2M; f= toluene, MW (P=250 W), 45 min.; g= Ac_2O/Py (P=150 W), 10 min.

Scheme 1.

metal catalyst and (*R*)-(+)-1,1′-bi-2-naphthol, as the chiral auxiliary.[6] Two different silyloxydienes **4** were employed, the cyclohexanone protected derivative giving the best results both in terms of enantioselectivity and yield. Enantiomeric excess and absolute configuration of the C-5 stereogenic center of **5** were determined by ^{1}H-NMR analysis of the corresponding MTPA esters according to the modified Mosher's method.[7]

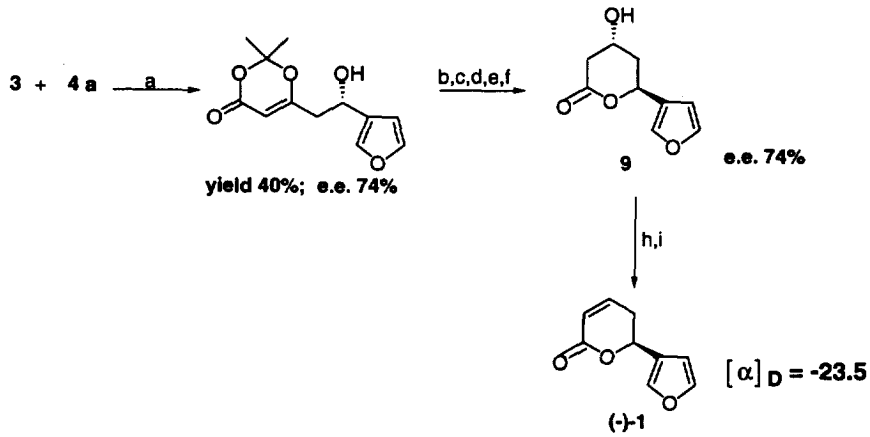
One-pot deprotection and conversion of **5b** into the open chain compound **6** was performed by a new simple procedure involving MW irradiation in a kitchen oven (P=250 watt) for 15 minutes. Reduction of **6** with a $Et_2BOMe/NaBH_4$ system according to Prasad methodology[8] afforded diol **7** with a very high degree of diastereoselectivity: in fact, as supported by NMR data, the syn-diol was obtained as by far the predominant product (syn/anti ratio=99/1).

The formation of the pyranone ring took place by a three-step sequence involving carefully controlled alkaline hydrolysis and acidification; the resulting crude dihydroxyacid, as a suspension in toluene, was subjected to MW irradiation to give the lactone **8** (58% overall yield from **7**).

The value of enantiomeric excess (>95%), determined by ^{1}H-NMR analysis of the corresponding MTPA ester of **8**, showed that no significant epimerization of C-3 and C-5 stereogenic centres had taken place in the course of the reactions leading from **5** to **8**. Finally, the target compound **1** has been obtained as (+)-**1** by MW irradiation of a solution of **8** in Ac_2O/Py.

The enantiomer (−)-**1** was obtained by the same sequence involving in the first step the asymmetric aldol condensation in the presence of (*S*)-(−)-1,1′-bi-2-naphthol (Scheme 2).

It is noteworthy that 6-substituted-3-hydroxy lactone **9** possessing the appropriate stereochemical



a= Ti(OiPr)$_4$/(S)-(+)-binaphthol; b= toluene, MeOH (12 equiv.), MW (P=250 W), 15 min.; c= Et_2BOMe, $NaBH_4$; d= NaOH/EtOH; e= H_2SO_4 2M; f= toluene, MW (P=250 W), 45 min.; h=Ac_2O/Py, i=DBU/$CHCl_3$

Scheme 2.

relationship between the substituents in the 4 and 6 positions of the pyranone ring, can be considered a synthetic analogue of compactin, a well-known inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase.[9]

Acknowledgements

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