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TETRAHEDRON: *ASYMMETRY*

Efficient synthesis of chiral non-racemic 6-(furan-3-yl)-5,6-dihydro-pyran-2-ones

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Abstract

The title compounds are accessible in high yields and enantioselectivities by a five-step sequence involving in the key-step asymmetric aldol condensations of masked acetoacetic esters to 3-formyl furan.

The noteworthy synthetic utility of 6-(furan-3-yl)-pyran-2-one derivatives of type **1** has been recently[1–3] confirmed by their employment as key-intermediates in the preparation of pyranofuranones **2** both in racemic and enantiomerically enriched form. Investigations on the structure–activity relationship[2,4] have shown that the pyranofuranone moieties of **2a**,**b** represent the pharmacophoric groups, respectively, of manoalide[5] and cacospongionolide B,[6] two naturally occurring marine compounds, characterized by powerful antiinflammatory properties (Fig. 1).

The logical consequence of these findings was a strong demand of a rapid, highly efficient and stereoselective approach to products of type **2**. We now report that key-intermediates **1** are accessible in very good yield and high enantiomeric excess through a simple five-step sequence starting from the easily available 3-formyl furan **3** and masked acetoacetic esters **4** (Scheme 1).

The crucial point of our strategy was represented by the generation of the stereogenic center in the first step by an enantioselective aldol condensation and, therefore, a preliminary investigation was planned. We have found that a careful choice of the experimental conditions allows a noticeable improvement of Sato's procedure,[7] involving Ti(IV)-catalyzed addition of silyloxydienes of type **4** to aldehyde **3** in the presence of (*R*)-(+)-binaphthol, as a chiral auxiliary (Table 1).

As clearly pointed out, the best results have been obtained by using equivalent amounts of starting material **3** and Ti(IV)–Binol complex (entries **c**, **d** and **g**), although very satisfactory yields and e.e.s can be observed in the presence of only 0.5 equivalents of the catalytic system (entry **f**). The introduction of a methyl group in 5 position of silyloxydiene **4** resulted in a noticeable lowering of the yields; however, **5c** could be obtained in good enantiomeric excess (entry **j**).

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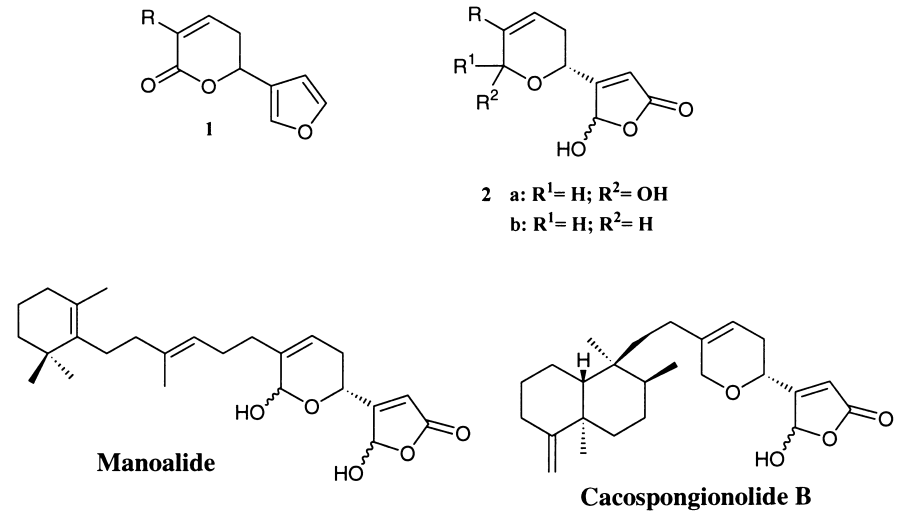
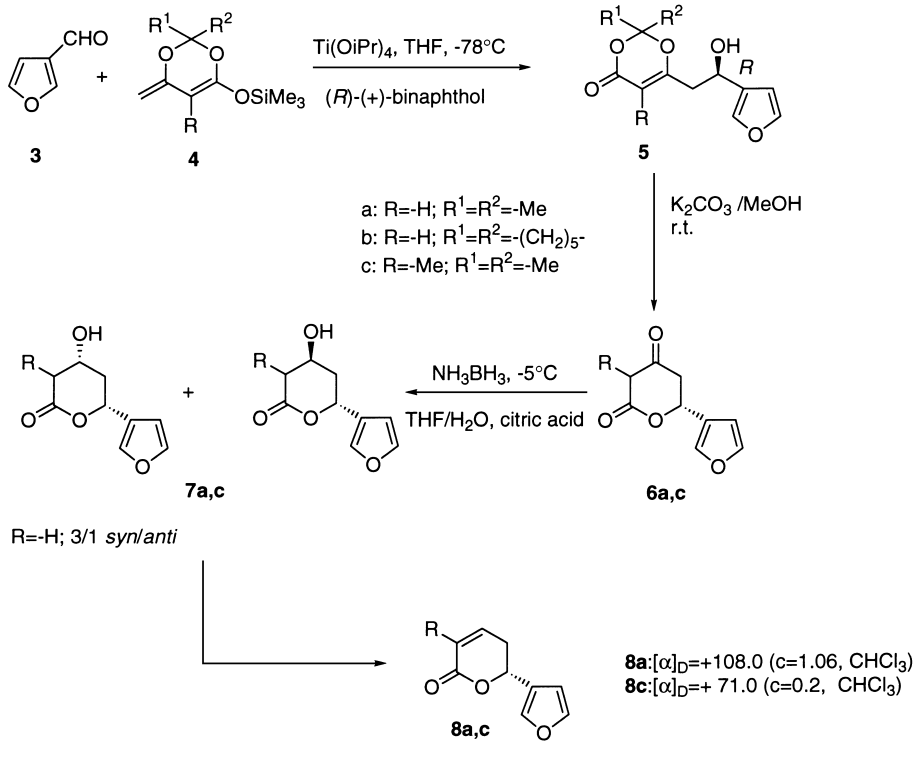


Figure 1.



Scheme 1.

Treatment of enantiomerically enriched **5a** (91% e.e.) and **5c** (90% e.e.) with methanolic potassium carbonate afforded β-ketolactones **6a** and **6c** in nearly quantitative yields and, then, the reduction of the ketone functionality with an NH_3BH_3 complex led to β-hydroxylactones **7a**,**c** in >90% yields (^{1}H NMR analysis). As regards the stereochemical outcome of the reduction, **7c** was obviously obtained as a very complex mixture of diastereoisomers, while ^{1}H NMR analysis of crude **7a** indicated the formation of a 3:1 *syn*:*anti* mixture. The diastereoisomeric ratio was determined through the careful integration of the

Table 1
Enantioselective aldol condensation of silyloxydienes **4** to aldehyde **3**

Entry	R^1	R^2	R	Ti(IV)/Chir.aux.	Yield[a] (%)	e.e.[b] (%)
a	Me	Me	H	0.17/0.17 eq.	42	80
b	Me	Me	H	0.50/0.50 eq.	65	89
c	Me	Me	H	1.00/1.00 eq.	81	91
d	Me	Me	H	1.00/1.00 eq.	76	91[c]
e	$-(CH_2)_5-$	$-(CH_2)_5-$	H	0.17/0.17 eq.	59	87
f	$-(CH_2)_5-$	$-(CH_2)_5-$	H	0.50/0.50 eq.	89	94
g	$-(CH_2)_5-$	$-(CH_2)_5-$	H	1.00/1.00 eq.	92	>95
h	Me	Me	Me	0.17/0.17 eq.	40	67
i	Me	Me	Me	0.50/0.50 eq.	41	72
j	Me	Me	Me	1.00/1.00 eq.	50	88

[a] All the yields refer to isolated chromatographically pure compounds and are calculated on starting material **3**
[b] E.es have been determined by ^{1}H-NMR analysis (400MHz) on the corresponding MTPA esters. Absolute configurations have been assigned through the modified Mosher procedure[8].
[c] In this entry (*S*)-(-)-binaphthol was used as chiral auxiliary and (*S*)-aldol was obtained.

signals relative to the 6-H proton (*syn*: 5.50 δ, dd, J=11.9 Hz, 2.9 Hz; *anti*: 5.73 δ, dd, J=10.9 Hz, 3.2 Hz).

In every case, both hydroxylactones **7a**,**c**, without any purification, were directly converted into α,β-unsaturated lactones **8a**,**c** in >85% yield by an already known procedure[1] involving first treatment with Ac_2O/Py (leading to the corresponding β-acetoxylactones) and then base-catalyzed AcOH elimination. Enantiomeric excesses of **8a**† (87%) and **8c** (92%) were determined by ^{1}H NMR analysis in the presence of Eu(hfc)$_3$, as shift reagent, by careful integration of the signals relative to the proton in 4 position of the furan nucleus.

Obviously, the employment of *S*-(−)-binaphthol, as a chiral auxiliary, in the first step of the sequence (entry **d**, Table 1) has allowed the final product, *S*-**8a**, to be obtained with comparable yield and enantiomeric excess.

Acknowledgements

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† The $[\alpha]_D$ value reported in Scheme 1 for compound **8a** represents a correction of the value previously reported[3] for the same compound.

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