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Efficient synthesis of enantiomerically pure dihydropyrans

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Abstract—*cis*- and *trans*-2-Substituted-3,6-dihydro-2*H*-pyran-3-ols have been prepared via an aldol condensation/ring-closing metathesis/enzymatic resolution sequence. The process can be scaled up to yield gram quantities of enantiomerically pure material.

Dihydropyrans are essential structural motifs that make up the backbone of synthetic and naturally occurring ionophores and polymer macrolides.[2] They are also key intermediates in the synthesis of many complex marine toxins; for example, dihydropyran (**1**) is one of the building blocks in the multistep synthesis of brevetoxins and ciguatoxin fragments (Fig. 1).[3,4] Dihydropyrans are typically prepared by Claisen rearrangement,[5] anionic,[6] cationic,[7] radical,[8] transition metal catalyzed,[9] allylation-Prins,[10] and hetero Diels–Alder[11] cyclizations.

The Grubbs ruthenium and Schrock molybdenum based ring-closing metathesis (RCM) reactions have started a renaissance in the preparation of carbocycles of various sizes.[12] The popularity of these technologies has led to the development of a variety of industrial processes, as well as to the advent of a recyclable polymer-supported catalyst[13] and efficient chiral catalytic systems.[14] Crimmins et al. recently reported an elegant synthesis of chiral dihydropyrans via an auxiliary-based asymmetric aldol condensation followed by an RCM reaction.[15,16] As part of our program directed at the development of pharmaceutically active carbohydrate analogs, we needed a synthetic route that could provide gram quantities of enantiomerically pure *cis*- or *trans*-2-substituted-3,6-dihydro-2*H*-pyran-3-ols from readily available starting materials.[17] As such, we envisioned that a tandem racemic aldol condensation/RCM followed by an enzymatic resolution could provide an economic alternative to the aforementioned methodologies (Scheme 1).

Treatment of **4**[18] with LDA at −78 °C, followed by slow addition of acrolein afforded the *threo* and *erythro* hydroxy esters **5** as a 2:1 mixture of diastereomers, which reacted smoothly with Grubbs' catalyst in toluene to give racemic *cis*- and *trans*-dihydropyrans **6** and **7** (Scheme 2). A simple chromatographic separation of these diastereomers followed by incubation with a series of commercially available enzymes provided enantiomerically pure dihydropyrans (−)-**6**, (+)-**7**, (−)-**8**, and (−)-**9** (Tables 1 and 2).[19] Excellent resolution was achieved in many cases and the Amano PS-C-1 lipase showed the highest turnover rate.[20] Using this process, all four dihydropyran isomers (−)-**6**, (+)-**7**, (−)-**8**, and (−)-**9** could be isolated in >99% ee. $LiAlH_4$ reduction of these dihydro-2*H*-pyran-2-carboxylic esters afforded the corresponding optically active dihydropyrandiols (+)-**10**, (+)-**11**, (−)-**10**, and (−)-**11** (Scheme 3).[21,22]

Dihydroxylation of ester (−)-**8** (OsO_4, NMO, THF-*t*-BuOH, H_2O) afforded the diastereomeric triol isomers (+)-**12** and **13** in a 6:1 ratio (Scheme 4). The same selectivity was observed for the dihydroxylation of (−)-**6** to **14** and (−)-**15**. Alternatively, dihydroxylation of the esters (+)-**7** and (−)-**9** to the triols (+)-**16** and (+)-**17**

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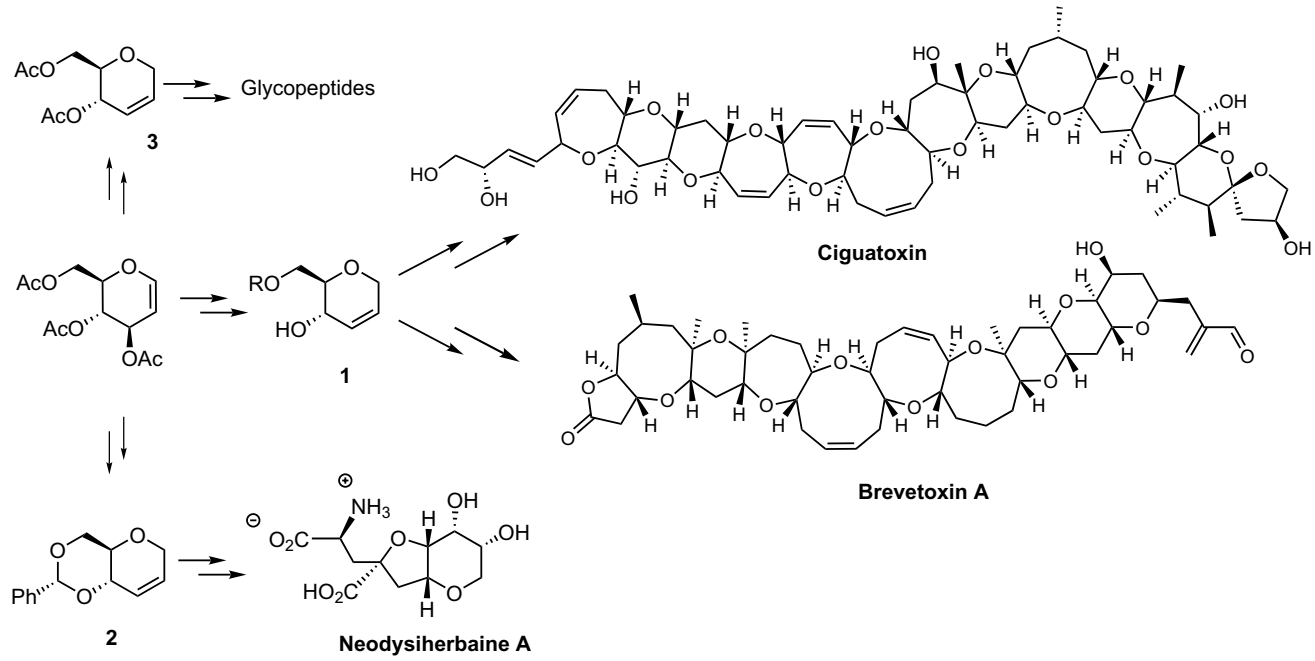
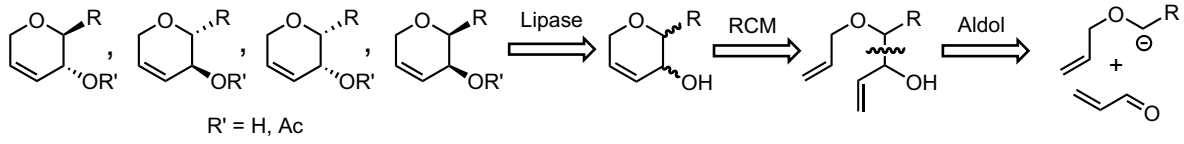
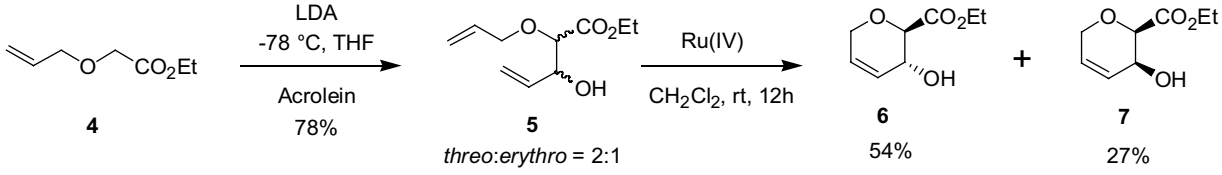


Figure 1. Selected synthetic applications of dihydropyrans.

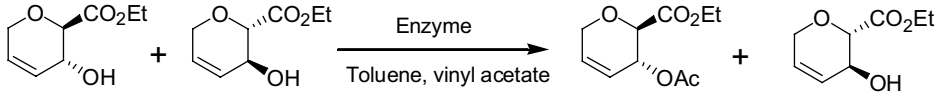


Scheme 1.



Scheme 2.

Table 1. Enzymatic resolution of racemic-**6**[a]



Entry	Enzyme	Time (h)	% Ee_s[b]	Yield (−)-**8** (%)	% Ee_p[c]	Yield (−)-**6** (%)	*E*-Value
1	Altus 27	14	>99.5	47	95.3	49	>247
2	CHIRAZYME L-5	24	>99.5	47	88.5	48	>96
3	CHIRAZYME L-10	24	>99.5	48	98.8	47	>992
4	AMANO PS-C-1	4	>99.5	46	99.4	47	>1993

[a] The reaction was monitored and stopped once 50% of the substrate was consumed.[24] Products were isolated by chromatography.
[b] Ee_s: enantiomeric excess of alcohol (−)-**6**.
[c] Ee_p: enantiomeric excess of acetate (−)-**8**.