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Efficient synthesis of enantiomerically pure dihydropyrans

Bor-Cherng Hong,[a,*] Zhong-Yi Chen,[a] Arumugam Nagarajan,[a] Kottani Rudresha,[a] Vishal Chavan,[a] Wei-Hung Chen,[a] Yea-Fen Jiang,[a] Shuo-Cang Zhang,[a] Gene-Hsiang Lee[b,†] and Sepehr Sarshar[c]

[a]*Department of Chemistry, National Chung Cheng University, Chia-Yi 621, Taiwan, ROC*
[b]*Instrumentation Center, National Taiwan University, Taipei 106, Taiwan, ROC*
[c]*Auspex Pharmaceuticals, Inc. 1261 Liberty Way, Suite C, Vista, CA 92081-8356, USA*

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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**

Keywords: Aldol; Metathesis; Synthesis; Enzyme; Dihydropyran.
* Corresponding author. Tel.: +886 52428174; fax: +886 52721040; e-mail: chebch@ccu.edu.tw
† See Ref. 1.

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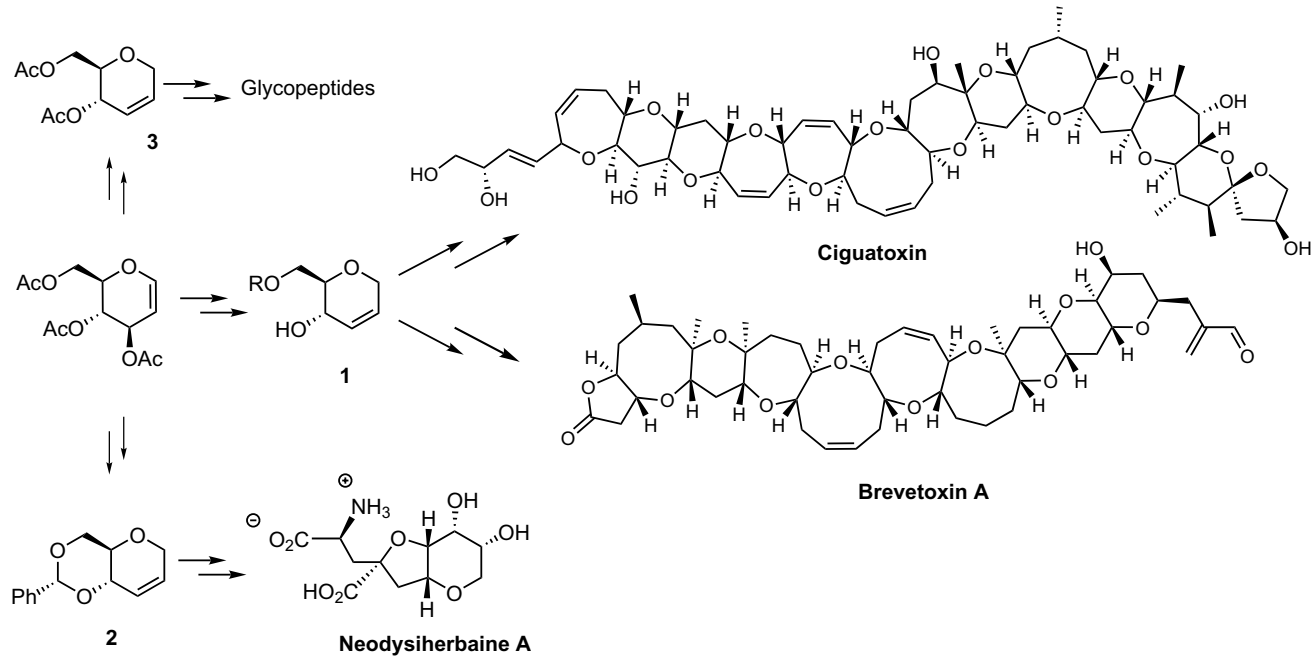
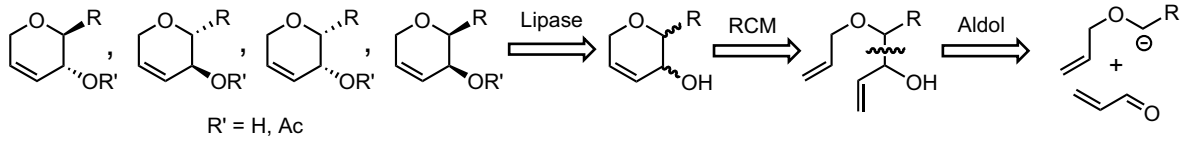
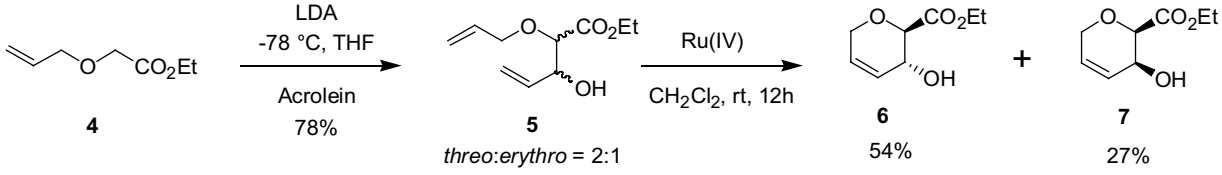


Figure 1. Selected synthetic applications of dihydropyrans.

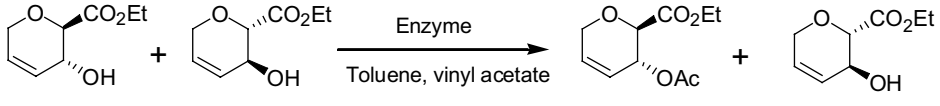


Scheme 1.



Scheme 2.

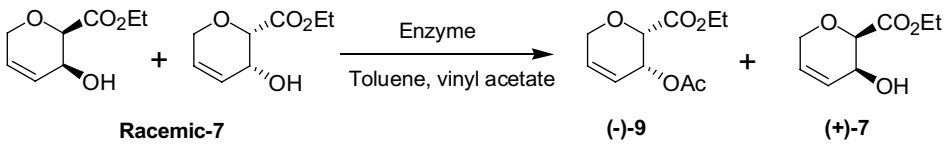
Table 1. Enzymatic resolution of racemic-**6**[a]



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**.

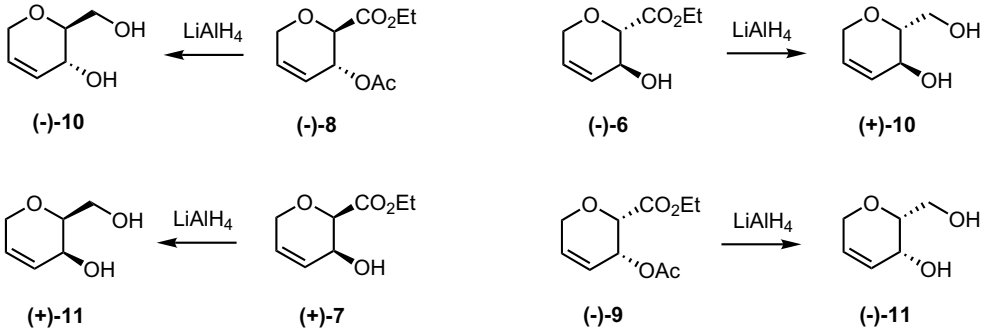
Table 2. Enzymatic resolution of racemic-7[a]



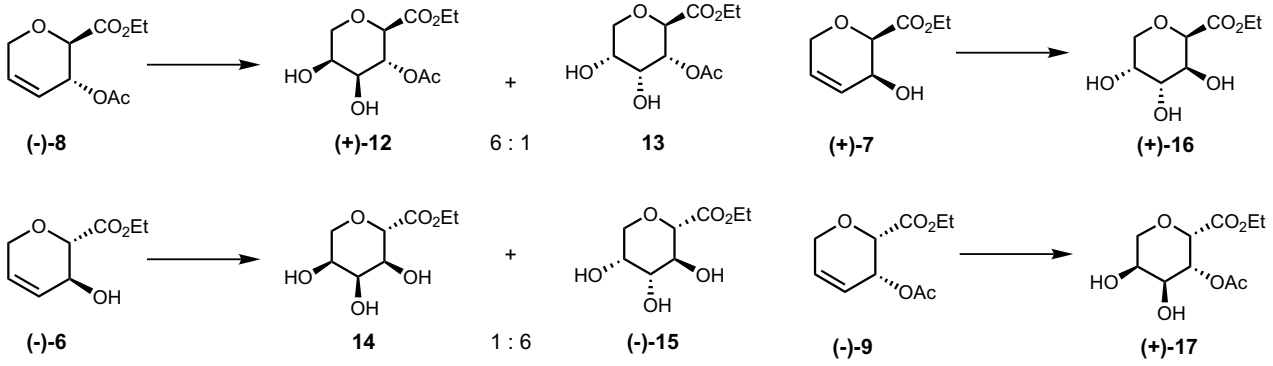
Racemic-7 (-)-9 (+)-7

Entry	Enzyme	Time (h)	% Ee_s[b]	Yield (−)-**8** (%)	% Ee_p[c]	Yield (−)-**6** (%)	*E*-Value
1	Altus 27	14	98.8	49	>99.5	48	>2049
2	CHIRAZYME L-3	34	>99.5	48	>99.5	48	>2393
3	CHIRAZYME L-5	20	>99.5	48	>99.5	49	>2393
4	CHIRAZYME L-10	8	>99.5	48	>99.5	47	>2393
5	AMANO PS-C-1	4	>99.5	47	>99.5	47	>2393
6	AMANO PS-C-2	4	>99.5	45	>99.5	48	>2393
7	AMANO PS-D-1	38	>99.5	48	>99.5	49	>2393
8	AMANO AK	38	>99.5	48	>99.5	48	>2393

[a] The reaction was monitored and stopped once 50% of the substrate was consumed. Products were isolated by chromatography.
[b] Ee_s: enantiomeric excess for the remaining alcohol (+)-**7**.
[c] Ee_p: enantiomeric excess of acetate (−)-**9**.



Scheme 3.



Scheme 4. Reagents and conditions: OsO_4, NMO, THF-*t*-BuOH–H_2O, rt, 96 h.

was completely stereoselective.[23] This is presumably due to the high transition state energy for the formation of the all-*cis* triol esters. The structure of triol ester (+)-**12** was assigned unambiguously by its single crystal X-ray analysis (Fig. 2).

In summary, enantiomerically pure *cis*- and *trans*-2-substituted-3,6-dihydro-2*H*-pyran-3-ols have been prepared via a sequence of aldol condensation/RCM/enzymatic resolution. These dihydropyrans can be readily transformed into their 6-deoxysugar counterparts using

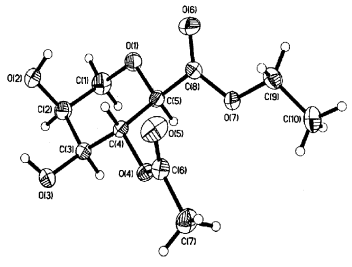


Figure 2. ORTEP plots for X-ray crystal structure of (+)-**12**.

a traditional dihydroxylation protocol. Ultimately, the most desirable route for large-scale preparation of these dihydropyrans should not involve any chromatographic separation. Further application of this methodology is underway in our laboratories.[25]

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.12.128.

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