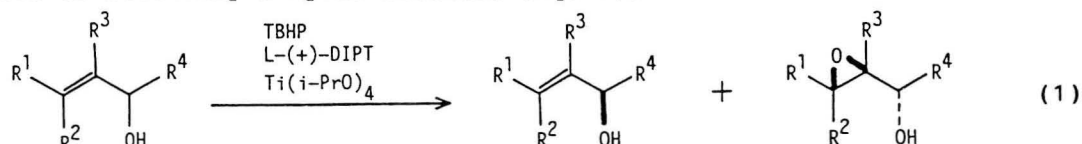


A Highly Efficient Synthesis of Prostaglandin ω -Chain Precursors

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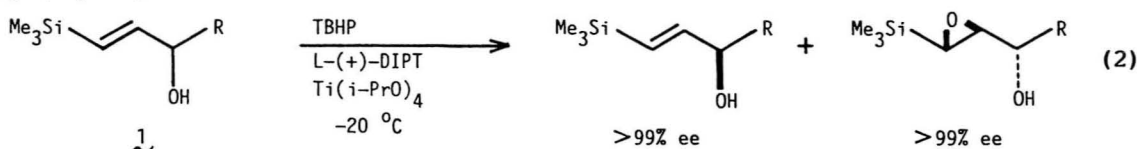
Kinetic resolution of γ -tributylstannyl allylic alcohols by the Sharpless asymmetric epoxidation proceeds with synthetically satisfactory rate differences for the two enantiomers, thus providing a highly efficient method for the synthesis of prostaglandin ω -chain.

Kinetic resolution of racemic allylic alcohols by the Sharpless asymmetric epoxidation has been widely used to prepare optically active erythro- β,γ -epoxy alcohols or secondary allylic alcohols (Eq. 1).¹⁾



Recently we have been interested in the kinetic resolution of the racemic allylic alcohols possessing a heteroatom substituent at olefinic position as well as the application of the reaction products in organic synthesis.²⁻⁴⁾

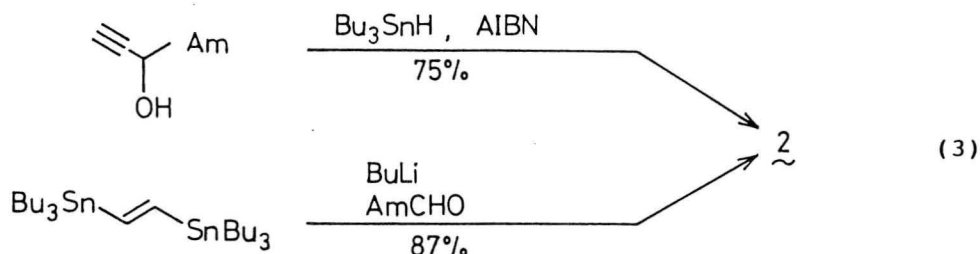
The kinetic resolution of γ -trimethylsilyl allylic alcohols 1 has been found to proceed with very large rate differences for the two enantiomers in comparison with the usual secondary allylic alcohols, to provide both the epoxy alcohols and the allylic alcohols with more than 99% enantiomeric purity, respectively (Eq. 2).²⁾



With this result in hand, our attention has been directed to the kinetic resolution of the γ -tributylstannyl allylic alcohol 2 since it would provide a direct and very short route to optically pure (S)-2 and eventually the γ -iodo allylic alcohol (S)-3, both of which can be used as the ω -chain units for the synthesis of naturally occurring prostaglandin (PG) in the conjugated addition approaches.⁵⁾ Reported herein is the realization of such expectation.⁶⁾



The starting allylic alcohol 2 can be obtained in large quantities by the hydrostannation of 1-octyn-3-ol with Bu_3SnH in the presence of a catalytic amount of AIBN followed by the separation of the co-produced (Z)-isomer (E:Z = 7:1) by column chromatography on silica gel,⁷⁾ or specifically by the reaction of the vinylstannane prepared from (E)-1,2-bis(tributylstannyl)ethylene and BuLi ⁸⁾ with hexanal (Eq. 3). Table 1 summarizes the results of the kinetic



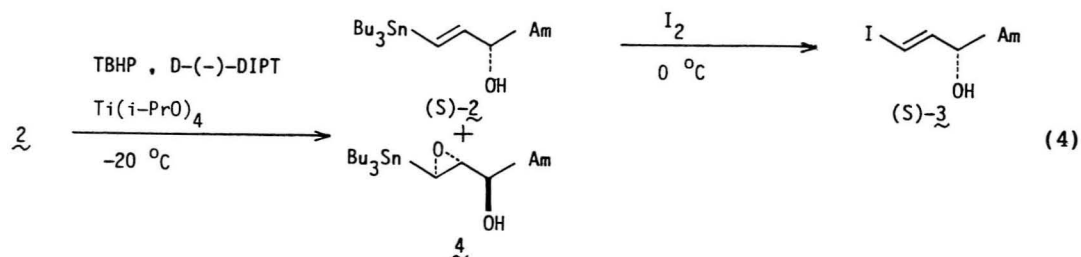
resolution of 2 using D-(-)-diisopropyl tartrate (D-(-)-DIPT) as a chiral source. It can be seen from the Table that the relative rate of fast and slow

Table 1. Results of the kinetic resolution of 2

Run	Reaction condition ^{a)}			Optical purity/% ee	
	Ratio <u>2</u> /Ti(i-PrO) ₄ /D-(-)-DIPT	Concentration mol l ⁻¹	Reaction time/h	(S)- <u>2</u> ^{b)}	<u>4</u> ^{c)}
1	1.0/1.0/1.2	0.1	4.0	94.5 ^{d)}	91.7 ^{d)}
2	1.0/1.0/1.2	0.2	4.5	>99	84.0
3	1.0/0.2/0.24 ^{e)}	0.5	4.0	>99	80.0

a) Reaction was carried out by using 1.5 equiv. of TBHP at -20 °C in CH_2Cl_2 .
 b) Determined by ^1H NMR analysis after converting into MTPA ester of (S)-3.
 c) Determined by ^1H NMR analysis after converting into MTPA ester of (R)-3 prepared by the reaction of 4 with Bu_3SnLi ⁹⁾ in THF followed by treatment with I_2 .
 d) These values indicate that the relative rate of fast and slow reacting enantiomers is about 80 based on the equation which relates the relative rates to the optical purities of (S)-2 and 4.¹⁾ Total yields of (S)-2 and 4 were >95% (^1H NMR analysis).
 e) Crushed molecular sieves 3A were present.

reacting enantiomers of 2 is not so great as for 1, but have the synthetically satisfactory magnitude of about 80. Thus, the kinetic resolution of 2, usual work-up, and separation of the resulting epoxide 4 by column chromatography on silica gel (2; $R_f = 0.46$, 4; $R_f = 0.41$ (3:1 hexane- Et_2O) afforded (S)-2, $[\alpha]_D^{25} +3.1^\circ$ (c 1.31, CHCl_3), with >99% ee in 38-42% yield (based on racemic 2) (Eq. 4). Noteworthy also is the fact that the kinetic resolution also proceeds effectively by using 20% catalyst in the presence of molecular sieves (run



3).¹⁰⁾ The alcohol (S)-2 thus obtained was converted into (S)-3, $[\alpha]_D^{25} +9.8^\circ$ (c 1.90, MeOH), (lit.¹¹⁾ $[\alpha]_D^{24} +9.87^\circ$ (c 1.57, MeOH), quantitatively by treatment with I_2 in ether (Eq. 4).¹²⁾ The alcohol (S)-3 was obtained more conveniently by treatment of the crude reaction mixture of (S)-2 and 4 with I_2 directly after the kinetic resolution, since the epoxy alcohol 4 was converted into unidentified product(s) which have very small R_f value, thus (S)-3 can be readily isolated by passing through a short silica gel column.

Similarly, the alcohol (S)-6¹³⁾ and (R)-8, which can be used as the ω -chain for the synthesis of the analogs of naturally occurring PG,¹⁴⁾ were synthesized by starting with racemic 5 and 7, respectively. The yields, $[\alpha]_D$ values, and 1H NMR data of (S)-6 and (R)-8 thus prepared are summarized in Table 2.



Table 2. Specific rotations, 1H NMR data, and overall yields of (S)-6 and (R)-8^{a)}

	$[\alpha]_D^{25}$ (c in $CHCl_3$)	1H NMR (CCl_4 , Me_4Si)	Yield ^{b)} /%
(S)- <u>6</u> ^{c)}	$+11.8^\circ$ (1.17)	δ 0.70-2.04(m, 11H, $5CH_2$ and CH), 2.86 (br s, 1H, OH), 3.72(t, $J=6.4Hz$, 1H, CHO), 6.16(d, $J=15.6Hz$, 1H, ICH), 6.46 (dd, $J=15.6, 6.4Hz$, 1H, $CH=CHI$).	41
(R)- <u>8</u> ^{c)}	-8.8° (1.41)	δ 3.03(br s, 1H, OH), 3.56-3.98(m, 2H, CH_2), 4.30(dt, $J=7.0, 4.0Hz$, 1H, CHO), 6.38(d, $J=16.0Hz$, 1H, ICH), 6.46-6.67 (m, 1H, $IC=CH$), 6.57-7.28(m, 5H, OPh).	40

a) Reaction was performed as follows: crushed molecular sieves 3A, 0.2 equiv. of $Ti(i-PrO)_4$, 0.24 equiv. of D-(-)-DIPT, 1.0 equiv. of the substrate and 1.5 equiv. of TBHP in dry CH_2Cl_2 (2 ml/mmol) were stirred at $-20^\circ C$ for 4 h. After work-up, the crude mixture was treated with I_2 in Et_2O at $0^\circ C$ and the iodide was isolated by column chromatography on silica gel. b) Overall yield from racemic 5 and 7, respectively. c) Optical purities were $>99\%$ ee determined by 1H NMR analysis of the corresponding MTPA esters.

In summary, kinetic resolution of γ -tributylstannyl allylic alcohols by the Sharpless process affords a new method for preparation of the ω -chain of naturally occurring PG and their analogs. The procedure is operationally simple and can be applied in large scale production.

A part of this work was supported by the Grant-in-Aid for Special Project Research from the Ministry of Education, Science and Culture (No. 61125005).

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(Received May 7, 1987)