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SYNTHESIS OF 1-SUBSTITUTED (S)-4-ACETOXY-1-PENTEN-3-ONES USING (S)-LACTIC ACID AS A CHIRAL SOURCE AND THEIR SYNTHETIC REACTIONS

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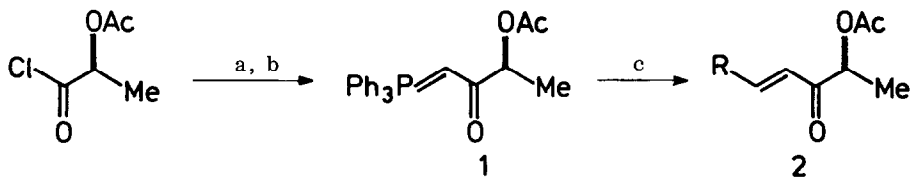
Ylide reaction of (S)-3-acetoxy-1-triphenylphosphoranylidene-2-butanone, derived from (S)-lactic acid, with aldehydes gives 1-substituted (S)-4-acetoxy-1-penten-3-one derivatives, which are shown to be transformed into useful chiral compounds by stereoselective reduction or the Johnson-Claisen rearrangement.

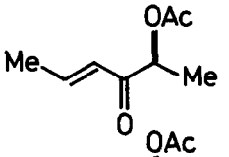
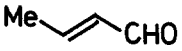
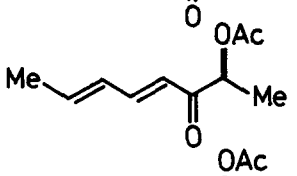
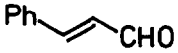
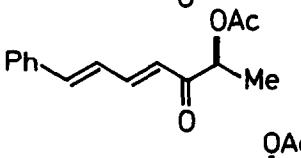
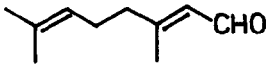
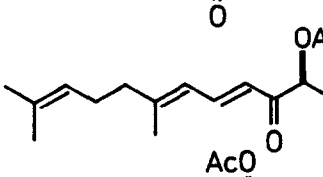
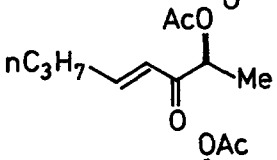
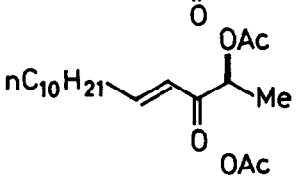
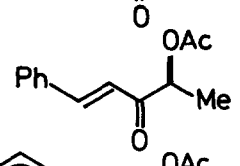
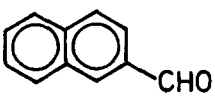
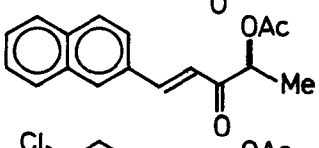
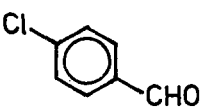
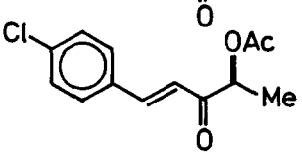
Exploratory study on specific or highly selective transformation of simple chiral natural products seems to be still warranted in view of the limited accessibility of chiral material.[1] For example, (S)-lactic acid derivatives, readily available in optically pure form, have been employed for chiral synthesis of useful compounds.[2] Herein we report ylide reaction of (S)-3-acetoxy-1-triphenylphosphoranylidene-2-butanone (**1**) with aldehydes to afford 1-substituted (S)-4-acetoxy-1-penten-3-ones (**2**), which are proved to be versatile chiral synthetic building block.

Synthesis and reaction of ylides having chiral centers at epimerizable positions are often hampered by racemization.[3] The procedure reported by Gandolfi and his coworkers[3a] is found applicable to the synthesis of **1** with slight modification. A benzene (5 ml) solution of (S)-2-acetoxypropionyl chloride[4] (0.72 g, 4.8 mmol) was added to a benzene solution (8 ml) of t-butyl triphenylphosphoranylideneacetate (prepared by titration of t-butoxycarbonylmethyltriphenylphosphonium bromide (4.40 g, 9.6 mmol) with sodium hydroxide aq solution and purified as usual) at 0 °C, and the resulting mixture was stirred for 16 h at room temperature. The precipitated phosphonium salt was filtered off, and the filtrate was concentrated under reduced pressure to give t-butyl (S)-4-acetoxy-3-oxo-2-triphenylphosphoranylidenepentanoate (2.86 g, quantitative yield). Subsequent hydrolytic decarboxylation was carried out, for example, by dissolving the ylide (0.32 g) in dichloromethane (1 ml) and trifluoroacetic acid (1 ml) and by heating the



a: Ph_3P=CHCOOtBu, b: CF_3COOH, c: RCHO

Table 1 Synthesis of 1-Substituted (S)-4-Acetoxy-1-penten-3-ones (2)

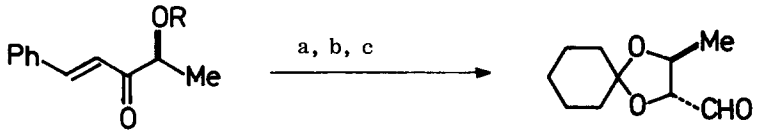
Run	Aldehyde	Product (% Yield)	$[\alpha]_D^{25}$ (°) ($CHCl_3$)
1	MeCHO	 **2a** (90)	-33.4
2		 **2b** (79)	-42
3		 **2c** (67)	-58
4		 **2d** (57)	-25
5	nC_3H_7CHO	 **2e** (71)	-28
6	$nC_{10}H_{21}CHO$	 **2f** (40)	-13
7	PhCHO	 **2g** (52)	-29
8		 **2h** (46)	-9
9		 **2i** (48)	-10

solution to reflux for 3 h. Thorough neutralization with aqueous sodium hydrogencarbonate, extraction with dichloromethane, concentration after drying, followed by column chromatography (silica gel, hexane-ethyl acetate (1:3), then methanol), gave **1** as a viscous oil (0.19 g, 91% overall yield), $[\alpha]_D^{20}$ -23.2° (c 1.11, $CHCl_3$).

The reaction of the ylide **1** with various aldehydes was carried out by heating the equimolar mixture of **1** and aldehyde in benzene at 60 °C. The products **2** were isolated by preparative TLC or column chromatography and the results are shown in Table 1. The newly generated C=C bond was mainly (>95%) (E) as revealed by ^1H NMR and IR. The enantiomeric purity of **2g** was estimated to be more than 95% by the ^1H NMR assay with a chiral shift reagent $Eu(TFC)_3$.

Synthetic usefulness of chiral enones **2** is shown in the following transformations.

Threo-Selective Reduction: Reduction of **2g** (R = Ac) with dimethylphenylsilane and tetrabutylammonium fluoride catalyst[5] followed by hydrolysis gave (2S,3S)-5-phenyl-4-pentene-2,3-diol as the major product (95% yield, 84% selectivity). The threo-selectivity was slightly improved to 87% by the reduction of **2g'** (R = THP) with diphenylmethylsilane. Acetalization (91% yield) of the diol, followed by oxidative cleavage of the C=C bond (78% yield), gave (2R,3S)-2,3-(cyclohexylidenedioxy)butanal (**3**), whose optical purity was estimated to be over 95% by transformation into the known (2S,3S)-2,3-(cyclohexylidenedioxy)butanenitrile.[2b] These are versatile intermediates for amino sugar synthesis.[2b,6]

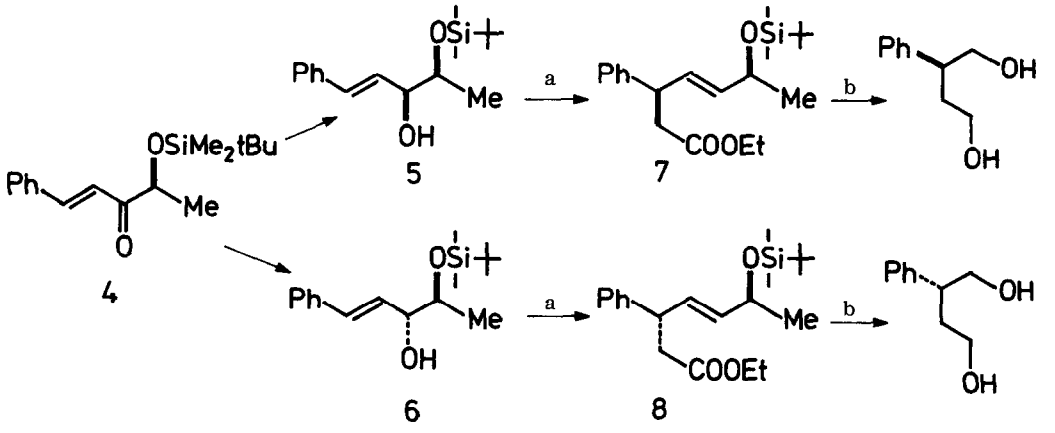


2g (R = Ac)
2g' (R = THP)

3

a: $PhMe_2SiH$ or Ph_2MeSiH, nBu_4NF, b: $(CH_2)_5C(OMe)_2$, $(Me_3SiO)_2SO_2$, Molecular Sieve 4A, c: $NaIO_4$, OsO_4

Chirality Transfer: The acetyl group of **2g** was converted to silyl protecting group by acidic hydrolysis and silylation. Reduction of the resulting **4** with sodium borohydride gave threo alcohol **5** ($[\alpha]_D^{20}$ -24.2° (c 1.02, MeOH) and erythro isomer **6** ($[\alpha]_D^{20}$ +40.0° (c 0.99, MeOH). These were readily separated by preparative TLC. The Johnson-Claisen rearrangement[7] of **5** and **6** gave **7** ($[\alpha]_D^{20}$ -9.4° (c 1.16, MeOH) and **8** ($[\alpha]_D^{20}$ +0.2° (c 1.04, MeOH)) in 66% and 70% yield respectively. The degree of the chirality transfer was checked by ozonolysis and subsequent reduction with sodium borohydride, and we obtained (S)-2-phenyl-1,4-butanediol ($[\alpha]_D^{20}$ +29.4° (c 0.72, MeOH); lit.,[8a] +29° (2%, MeOH)) from **7**, whereas (R)-2-phenyl-1,4-butanediol ($[\alpha]_D^{20}$ -28.5° (c 0.66, MeOH)) was produced from **8**. Thus, the chirality transfer by the Johnson-Claisen rearrangement in acyclic system[9] is proved to be over 97% irrespective of the original diastereomeric configuration. This methodology coupled with the stereoselective reduction[5] allows us to construct 1,4-asymmetric centers under stereocontrol.



a: $MeC(OEt)_3$, EtCOOH, 138 °C

b: O_3, MeOH, -78 °C; excess $NaBH_4$

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