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A Facile Synthesis of (2R,3E)-4-Iodobut-3-en-2-ol and (2S,3E)-4-Iodobut-3-en-2-yl chloroacetate

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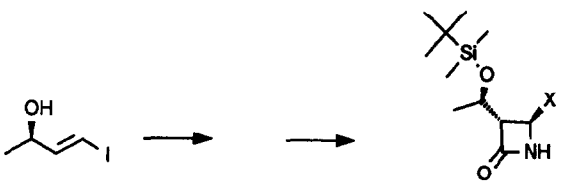
Abstract: (2R,3E)-4-Iodobut-3-en-2-ol ((**R**)-**1**) and (2S,3E)-4-Iodobut-3-en-2-yl chloroacetate ((**S**)-**7**) of high enantiomeric purity can be prepared by a lipase catalysed kinetic resolution of racemic (E)-4-Iodobut-3-en-2-yl chloroacetate (**7**). The alcohol (**R**)-**1** can be separated from the ester (**S**)-**7** by a simple distillation.

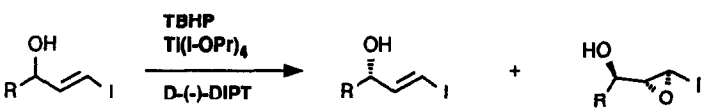
The enantiomerically pure building block (**R**)-**1** was required as an intermediate for synthesis of the azetidinone **2** (X = SPh).



(R)-1 **2**

The synthesis of γ-halo allylic alcohols was recently reviewed by Sato and Kobayashi.[1] The preparation of analogues of (**R**)-**1** was described by Sato et al,[2] who prepared the racemic alcohols **3a** - **3d** in three steps from acetylene. Kinetic resolution of **3** using the Sharpless asymmetric epoxidation gave a mixture of **4** and epoxides **5** (formed in 97-99 % ee) (Scheme 1). Treatment of the mixture with aqueous NaOH resulted in conversion of **5** to unidentified water-soluble by-products and allowed isolation of **4** in yields of 40-44 % (98-99 % ee) after purification by chromatography on silica gel.

Scheme 1



3 **a: R= amyl**
b: R= ethyl
c: R= cyclohexylmethyl
d: R= cyclopentyl

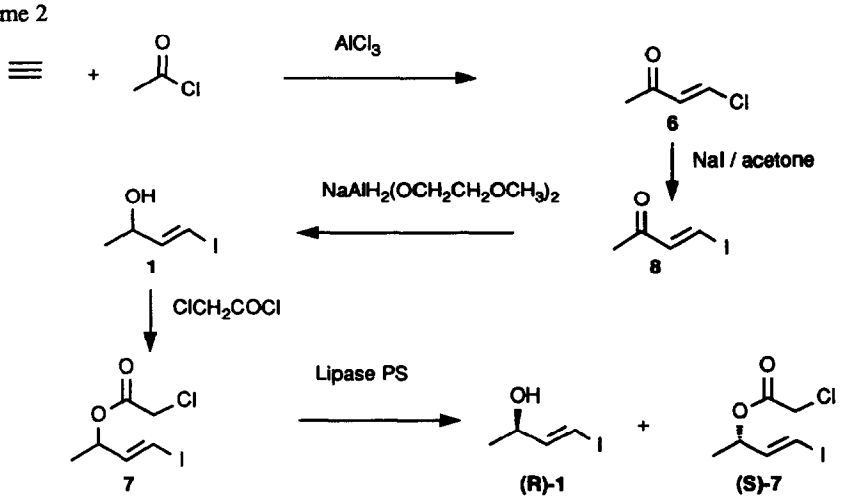
4 **5**

We wished to develop a kinetic resolution which could allow isolation of both enantiomers of

1. Several successful lipase-catalysed kinetic resolutions of substituted allylic alcohols or their corresponding esters are known,[3] in most of these a lipase from Pseudomonas was used. If the group attached to the olefin is of sufficient bulk, the selectivity of the lipase is high and we therefore decided to attempt lipase catalysed kinetic resolution of an ester of racemic **1**. It is known that the use of chloroacetate esters can bring about both an increase in the rate of lipase catalysed hydrolysis in comparison to that observed with simple acetate esters[4] and a simplification of the distillative separation of the products.[5]

Racemic (E)-4-iodobut-3-en-2-ol (**1**) was prepared in 2 steps from (E)-4-chlorobut-3-en-2-one (**6**), which is accessible from the reaction of acetylene with acetyl chloride.[6] Treatment of rac-**1** with $ClCH_2COCl/NEt_3$ afforded rac-**7**, which was subjected without purification to kinetic resolution using Lipase PS (Amano) in the two-phase system water/toluene (an increase in the selectivity of enzymatic hydrolysis brought about by use of toluene as a cosolvent has been reported by other authors).[7] Only 1 % by weight of lipase PS was required for an acceptable reaction-rate, the pH during the reaction was maintained at 7 by continuous addition of 1M NaOH. After 2.5 h the reaction rate dropped significantly and the mixture was filtered through Celite. The phases were separated and after evaporation of the toluene **(R)-1** was separated from the unreacted **(S)-7** by distillation at ca. 1 mm . **(R)-1** was obtained in 32 % yield (over 2 steps from **rac-1**) and 98 % ee (GC, Lipodex D). The residue contained **(S)-7** (ee 98 %, GC Lipodex D), which was isolated in 40 % yield after distillation (Scheme 2).

Scheme 2



The absolute configuration of **(R)-1** was confirmed by comparison with samples prepared by kinetic resolution of **1** via Sharpless epoxidation (using L-(+)-DIPT) and by reduction of **8** using BH_3 or catecholborane in the presence of the oxazaborolidine derived from (S)-2-(Diphenylhydroxymethyl)pyrrolidine and n-butylboronic acid, use of which has been shown to bring about the reduction of enones to (R)-alcohols.[8] The absolute configuration of **2** (X =

SPh) prepared from **(R)-1** was confirmed by preparation of an authentic sample via reaction of **2** (X = OAc) with PhSH/NaH; the displacement of the acetoxy group from **2** (X = OAc) is known to proceed with retention of configuration at C-4.[9]

The main advantages of this process are the high selectivity of the kinetic resolution and the easy separation of the product alcohol and the starting ester by distillation.

Experimental

Chemicals: Lipase PS was purchased from Amano (35500 u/g). (E)-4-chlorobut-3-en-2-one (**6**) was prepared from acetylene and acetyl chloride according to a described procedure.[6] Solvents and reagents were purchased from Fluka and used without further purification.

(E)-4-iodobut-3-en-2-one (8)
To a solution of (E)-4-chlorobut-3-en-2-one (50 g, 0.48 mol) in acetone (125 ml) was added sodium iodide (89.4 g, 0.6 mol). The mixture was stirred under an argon atmosphere for 1.8 h at 60 °C before evaporation under reduced pressure. Toluene (150 ml) was added to the residue and the mixture was washed with water (150 ml). The aqueous phase was extracted with toluene (3 x 100 ml) and the combined organic phases were dried ($MgSO_4$), filtered and evaporated under reduced pressure to yield 85 g (90 %) of a dark brown product, which was used immediately without purification.
^{1}H-NMR ($CDCl_3$, 300 MHz): 2.26 (d, 3H); 7.15 (d, 1H); 7.85 (d, 1H).

(E)-4-iodobut-3-en-2-ol (1)
Sodium dihydridobis(2-methoxyethoxy)aluminate (65 ml of 3.5 M solution in toluene, 0.228 mol) was added over 0.5 h to a solution of **8** (85 g, 0.43 mol) in toluene (800 ml) at -10 °C under argon. The reaction mixture was warmed to RT, stirred for 0.5 h and cooled to ca. 0 °C before addition of methanol (10 ml) followed by 10 % NaOH (40 ml). The phases were separated and the aqueous phase was extracted with toluene (200 ml). The combined toluene phases were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to afford 67.7 g (80 %) of crude product.
^{1}H-NMR ($CDCl_3$, 300 MHz): 1.3 (d, 3H); 2.05 (br.d, 1H); 4.23-4.36 (m,1H); 6.35 (d, 1H); 6.62 (dd, 1H).

(E)-4-iodobut-3-en-2-yl chloroacetate (7)
Triethylamine (11.07 g, 0.11 mol) was added to a solution of **1** (57.1 g, 0.25 mol) and DMAP (2.4 g, 20 mmol) in toluene (400 ml) at -5 °C under argon. The mixture was cooled to -10 °C before addition of chloroacetyl chloride (12.4 g, 0.11 mol) over 15 minutes. Further portions of both triethylamine (11.04 g, 0.11 mol) and chloroacetyl chloride (12.04 g, 0.106 mol) were added after 0.5 h and again after 1 h and the mixture was stirred at -5 °C for 1.5 h before

warming to RT. After 3 h the triethylammoniumchloride was filtered off and washed with toluene. The filtrate was washed with 0.1 M HCl (3 x 80 ml) and the combined aqueous phases were reextracted with toluene. The toluene phases were dried ($MgSO_4$), filtered and evaporated under reduced pressure to yield 72.4 g of crude product which contained ca. 10 % toluene by GC (95 % yield). This was used without further purification.
^{1}H-NMR ($CDCl_3$, 300 MHz): 1.38 (d,3H); 4.05 (s,2H); 5.30-5.43 (m, 1H);6.50-6.58 (m, 2H).

(2R,3E)-4-iodobut-3-en-2-ol ((R)-1) and (2S,3E)-4-iodobut-3-en-2-yl chloroacetate ((S)-7)
To a solution of crude (E)-4-iodobut-3-en-2-yl chloroacetate (7) (72 g) in toluene (136 ml) at RT were added water (680 ml) and lipase PS (680 mg). The mixture was stirred vigorously and maintained at pH 7 by continuous addition of 1M NaOH (total 117 ml). After 2.5 h the rate of the addition had decreased significantly; the reaction mixture was filtered through Celite, the phases were separated and the aqueous phase was extracted with toluene (2 x 200 ml). The combined toluene phases were evaporated under reduced pressure and the residue was distilled at 1 mm to give **(R)-1** (15.7 g, 32 % from **1**, b.p. 55 °C) and **(S)-7** (25.9 g, 40 % from **1**, b.p. 90 °C). Both **(R)-1** and **(S)-7** were of ee 98% (GC on Lipodex D).

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9. see for example, P. J. Reider and E. J. J. Grabowski, *Tetrahedron Letters*, **1982**, *23*, 2293.