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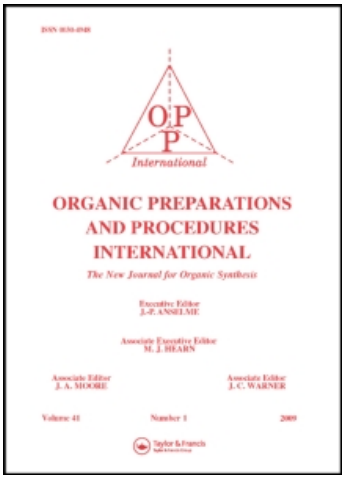

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN EFFICIENT LARGE SCALE PREPARATION OF (S)-1,1,2-TRIPHENYLETHANEDIOL 2-ACETATE

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To cite this Article Millar, A. , Mulder, L. W. , Mennen, K. E. and Palmer, C. W.(1991) 'AN EFFICIENT LARGE SCALE PREPARATION OF (S)-1,1,2-TRIPHENYLETHANEDIOL 2-ACETATE', Organic Preparations and Procedures International, 23: 2, 173 — 180
To link to this Article: DOI: 10.1080/00304949109458305
URL: http://dx.doi.org/10.1080/00304949109458305

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ORGANIC PREPARATIONS AND PROCEDURES INT. 23 (2), 173-180 (1991)

AN EFFICIENT LARGE SCALE PREPARATION OF (S)-1,1,2-TRIPHENYLETHANEDIOL 2-ACETATE

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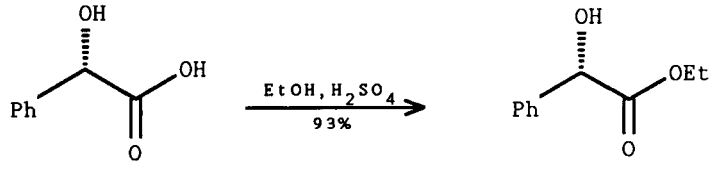
The stereo- and enantioselective syntheses of ß-hydroxy esters and acids, is an important aspect of natural product synthesis. Consequently the stereoselective aldol reaction is one of the most important carbon-carbon bond forming reactions available to the synthetic organic chemist.[1] Until recently achieving high degrees of stereoselectivity with α-unsubstituted enolates had proven elusive. However, several reports on the use of α-unsubstituted chiral enolates, providing good to excellent enantioselectivities, have recently appeared.[2,3] In



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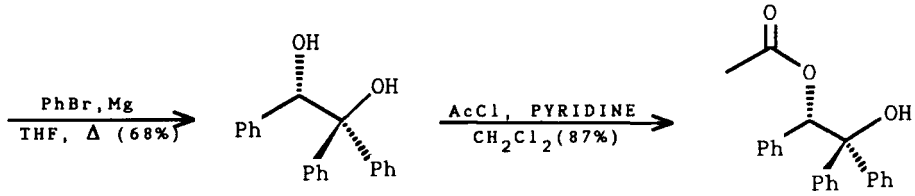

2 (S)-HYTRA

particular (R)- and (S)-1,1,2-triphenylethanediol 2-acetate [(R)- and (S)-HYTRA] have found practical use in the prepara-

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tion of a number of optically active natural and unnatural products.[4] The preparation of (R)- AND (S)-HYTRA has been described previously (Scheme).[5]

We required multi-kilo quantities of the title compound for the preparation of an optically active potential pharmaceutical agent. In our hands the literature procedure[5,6] gave the title compound in the reported yield, on the 20 to 50 g scale. However, the preparation of multi-kilo quantities required significantly larger scale runs. On scale-up (100 to 500 g), the Grignard reaction, using commercial or freshly prepared phenylmagnesium bromide and ethyl (S)-mandelate, provided the diol (2) in variable yields, ranging from poor (45%) to acceptable (60%). A major concern for scale up, was the inconsistency of the reaction product profile and the varying quantities of benzoin and benzophenone (10-40%) formed as by-products. Use of commercial phenyllithium provided similar yields to those reported[5] with little side-reaction, but required nine equivalents to obtain complete reaction.[7]

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The procedure described here employs a one-step Barbier reaction[8] in place of the Grignard reaction for the preparation of the chiral triphenylethanediol (2). This modification was found to provide **consistently** high yields of 2, (65-70%, after recrystallization[5,6]) while minimizing the impurities. Acetylation of the diol (AcCl/pyridine, CH_2Cl_2) provided the title compound in 55% overall yield and 100% ee. Approximately 2.5 equivalents of acetyl chloride were required to give consistently high conversions to product. It is presumed that this is a result of residual methanol associated with the diol[6c]. Diacetylation of 2 was not observed under these

conditions. Noteworthy is the development of a chiral HPLC assay for each of the isolated intermediates as well as the product. This clearly indicates that although the $[\alpha]_D$ values of the products vary, over several runs, the material is enantiomerically pure.

In summary, the Barbier reaction provides a process for the convenient, safe and economical large scale laboratory preparation of enantiomerically pure (S)-1,1,2-triphenylethanediol (2), the key intermediate in the preparation of the chiral acetate equivalent (S)-HYTRA. In our labs, this process has been carried out repeatedly on a 1 Kg scale and has also been used to prepare (R)-HYTRA (25 g scale).

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EXPERIMENTAL SECTION

Melting points were determined on a Mettler FB81 instrument and are uncorrected. ^{1}H NMR spectra were recorded on a Varian XL-200 (200 MHz) instrument using TMS (δ = 0.0 ppm). Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Gas chromatography was performed on a Varian 3500 capillary gas chromatograph, using a 15m DB-5 column. Infrared spectra were recorded on an Analect FX-6160 FTIR. HPLC were performed on an Econosil or Ultrasphere C-18, 5μ, 25cm column using a mobile phase of 10:25:65 MeOH:H_2O:CH_3CN at 1 ml/min and the detector at 225nm. Chiral HPLC were performed using a chiral stationary phase Chiracel-OF 25cm column at a column temperature of 60°C and for (1) a mobile phase of 5% IPA in hexane at 1 ml/min with the detector at 254nm, for (2) and (R) or (S)-HYTRA a mobile phase of 10% IPA in hexane at 1 ml/min with the detector at 225nm.
Mandelic acid, [$[\alpha]_D$ +151.5° (c = 2.8 in H_2O)], magnesium turnings, acetyl chloride and pyridine were purchased from Aldrich Chemical Co. THF and dichloromethane were purchased from J. T. Baker (Baker Analyzed Reagent). Bromobenzene was purchased from Great Lakes Chemical Co. Anhydrous 2B ethanol was purchased from Midwest Grain Products of Illinois and 98% Sulfuric acid (reagent grade) was purchased from E. M. Science. All reagents and solvents were used as received.

Ethyl (S)-Mandelate (1).[6a]- A 12 L, three-necked round-bottomed flask was equipped with a mechanical stirrer, a reflux condenser and a thermometer. The flask was charged with

500 g (3.3 mol) of mandelic acid, 4 L of absolute ethanol and 27 g of 98% sulfuric acid and the mixture heated at reflux (about 80°) for 4 hrs. The resultant solution was cooled to 0-5° and a 0-5° solution of 5N sodium hydroxide (approx. 80 ml) added until the pH of the reaction mixture was 7 to 7.5. The neutralized product solution was concentrated by vacuum distillation (55-60° at 28-30 mm/Hg), to about 750 ml, diluted with 1 L of ethyl acetate and washed with 1 L portions of water, saturated sodium bicarbonate solution and saturated brine solution. Drying over sodium sulfate, filtration and evaporation in vacuo provided (1) 550 g (93%) as a viscous liquid[9] which was 98.2% (1) and 1.3% EtOAc by VPC.

Chiral HPLC: (S)-enantiomer (12.2 min), 100%

(R)-enantiomer (13.4 min), none detected.

$[\alpha]D$ = +129.5° (c = 1.1, $CHCl_3$), lit.[6a] + 136° ($CHCl_3$).

^1H NMR(CD_3COCD_3): δ 1.13 (3H, t, J = 7.1 Hz), 4.10 (2H, m), 4.84 (1H, d, J = 5.0 Hz, exch. with D_2O) 5.20 (1H, d, J = 5.0 Hz collapses to singlet on exch. with D_2O), 7.25-7.50 (5H, m).

IR(neat): 1735 cm^{-1}.

(S)-1,1,2-Triphenylethanediol (2).- A 12 L, three-necked, round-bottomed flask equipped with a mechanical stirrer, an efficient reflux condenser and a pressure-equalizing addition funnel was flushed with nitrogen and charged with 295 g (12.1 mol) of magnesium turnings and 1 L of THF. Ethyl (S)-mandelate (500 g, 2.8 mol), bromobenzene (1.9 Kg, 12.1 mol) and THF (6 L) were charged to a nitrogen-flushed 10 L bottle and agitated. A 50 ml portion of the ethyl (S)-mandelate/bromobenzene/THF solution was charged to the flask containing the

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Mg/THF mixture[10] and the mixture was brought to a gentle reflux with vigorous stirring. Reflux was maintained until a yellow-brown color was observed.[11] The heat was removed and reflux maintained by addition of the balance of the ethyl (S)-mandelate/bromobenzene/THF solution[12] [**Caution: insufficient stirring can cause an uncontrollable rate of reflux**]. On completion of the addition, the mixture was maintained at reflux by application of heat for a further 16 hrs. After cooling, the mixture was quenched by slow transfer to a 22 L flask containing a stirring mixture of ice (5 Kg) and water (2.5 L). The aqueous mixture was adjusted to a pH of 1.5 with 5N hydrochloric acid solution and the product isolated by extraction with ethyl acetate (2 x 2 L). The ethyl acetate extracts were washed with 1 L portions of saturated sodium bicarbonate and saturated brine, dried ($MgSO_4$) and evaporated in vacuo. The resultant solid was recrystallized by dissolution in hot methanol (1.5 L). Cooling to room temperature initiates crystallization and addition of hexane (1 L) followed by stirring for 4 hrs at room temperature and 4 hrs at 0-5°C provides, after filtration, washing with hexane and vacuum drying, the product 550 g (68%) as colorless crystals, which was 97.2% pure with 2.5% benzoin by HPLC; mp 123.3-126.3°C, lit[6b] 128°C.

Chiral HPLC: (S)-enantiomer (11.6 min), 98.8%

(R)-enantiomer (9.9 min), none detected.

$[\alpha]_D$ = -212.1° (c = 1, $CHCl_3$), lit.[6b] -228° (c = 1.32, $CHCl_3$). The range of $[\alpha]_D$ values over numerous runs was -207° to -223° and in all cases the HPLC indicated no (R)-enantiomer present.

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^{1}H NMR(CD_3COCD_3): δ 4.46 (1H, s, exc. with D_2O), 4.66 (1H, d, J = 4.0 Hz, exch. with D_2O), 5.73 (1H, d, J = 4.0 Hz, collapses to singlet with D_2O), 6.95-7.40 (13H, m), 7.72 (2H, d, J = 7.7 Hz).

(S)-1,1,2-Triphenylethanediol 2-Acetate [(S)-HYTRA].- A 12 L, three-necked, round-bottomed flask equipped with a mechanical stirrer, an efficient reflux condenser, a pressure-equalizing addition funnel and a thermometer was flushed with nitrogen. The flask was charged with 550 g (1.9 mol) of (S)-1,1,2-triphenylethanediol, 3.5 L of dichloromethane and 450 ml of pyridine the stirring solution cooled to 0±5°. The addition funnel was charged with 365 ml (5.1 mol) of acetyl chloride and the acetyl chloride added dropwise at such a rate as to maintain the temperature at <15°[13]. After addition was complete the mixture was allowed to warm to room temperature and stirred for a further 20 hrs. The product was isolated by filtration, washed on the filter with methanol, water, methanol, and vacuum dried to give the product 550 g (87%) as colorless crystals, which was 98.1% pure with 1.2% (2) by HPLC; mp 242.2-243.7°C, lit[5] 237°C.

Chiral HPLC: (S)-enantiomer (5.8 min), 99.1%

(R)-enantiomer (5.0 min), none detected.

$[\alpha]_D$= -205.8° (c = 1, pyr), lit.[5] -213.8° (c = 1, pyr).

The range of $[\alpha]_D$ values over several runs was -205° to -213° and in all cases HPLC indicated no (R)-enantiomer present.

^{1}H NMR(DMF-d7): δ 1.92 (3H, s), 6.16 (1H, br s, exch. with D_2O), 6.71 (1H, s), 7.08-7.40 (13H, m), 7.55-7.65 (2H,m).

IR(KBr): 1721 cm^{-1}.

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7. Use of less than 9 equivalents of PhLi resulted in incomplete reaction, e. g. 6 equivs resulted in 16% starting ester unconsumed. For reasons of safety and economy, nine

equivalents of PhLi was not acceptable for large scale use.

8. For a review of the Barbier reaction see C. Blomberg, and F. A. Hartog, Synthesis, 18 (1977).
9. If left standing for several hours, the product would solidify but the liquid was generally used directly.
10. The most convenient method to transfer the large volumes of reagents is as follows: the 10 L bottle is stoppered with a two-hole rubber stopper through which is passed a teflon tube. The teflon tube is connected to the pressure equalizing addition funnel by use of a second rubber stopper. The ethyl (S)-mandelate/bromobenzene/THF mixture is then transferred in portions to the addition funnel using controlled application of nitrogen pressure on the 10 L bottle.
11. Vigorous stirring is essential for consistent initiation of the reaction. It is our experience that if the distinct yellow-brown coloration does not appear within 1 hr of reflux, it is best to quench the materials in the reaction vessel and start over with fresh magnesium. Several standard methods (I_2, $BrCH_2CH_2Br$, PhMgBr) failed to consistently initiate the reaction, and achieve the desired yields, if refluxing failed.
12. Addition will take approximately 4 hrs. During the initial stages of the reaction, the addition must be very slow and as the volume in the 12 L flask increases, the addition rate must be increased to maintain reflux. At all times efficient stirring must be maintained to avoid an uncontrollable rate of reflux.
13. Efficient stirring and cooling are necessary, since on initial addition of the acetyl chloride, a 20-30°C exotherm is observed and the reaction mixture becomes very thick due to precipitation of product and of pyridine hydrochloride. As addition continues, the slurry becomes thinner.

(Received June 7, 1990; in revised form October 18, 1990)

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