Notes

A Strategy for the Transformation of a Multifunctional Chiral Synthon of Moderate ee into an Enantiomerically Pure Synthetic Intermediate

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Introduction

The preparation of chiral compounds in enantiomerically pure form is an argument of increasing interest in the preparation of fine chemicals. The various techniques which can be applied to the *production* of chirality have been considered.[1] Among them, the possibility of obtaining pure enantiomers using crystallization as a key step is still the most successful way to reach the goal.[2] While the crystallization of diastereoisomeric salts is more often employed,[3] the direct crystallization of enantiomers from a racemic mixture is sometimes possible.

Horeau showed that by linking a chiral compound with a bifunctional nonchiral molecule the starting material itself can act as a chiral auxiliary forming diastereoisomeric couples which can be separated or recognized by physical or chemical means, thus allowing the analysis of the enantiomeric purity of the starting material or separation of diastereoisomer and then recovery of the enantiomers in enriched form.[4] This method has been widely used in determining the enantiomeric excess of a mixture. For example a nonracemic chiral alcohol derivatized with a bicarboxylic acid will give rise to two enantiomeric esters and a *meso* form. Their ratio will tell the enantiomeric purity of the starting material. While this technique has been often considered for analytical purposes,[5] only seldom it has been applied to the preparative enrichment of a nonracemic mixture. Fleming recently used the diester obtained from oxalyl chloride and a methylcarbinol to prepare, after crystallization of the diastereoisomeric mixture and hydrolysis, the starting alcohol in enantiomerically pure form.[6]

Results and Discussion

The application of the above technique in the synthetic sequence requires (i) generation of chirality (resolution, dissymmetrization, asymmetric synthesis) to give an enantiomerically enriched compound and (ii) derivatization of the chiral compound with the bifunctional nonchiral material which will allow, after crystallization and hydrolysis, for completion of the enantiomers separation. This methodology has not been applied in our knowledge to multifunctional compounds. We reasoned that the second part of the process (derivatization and hydrolysis) will not result in an additional step when multifunctional compounds are used, if the derivatization (necessary for diastereoisomers formation) acts at the same time also as a functional group protection and the bifunctional molecule enriched in one enantiomer thus obtained is used in a bi-directional synthesis not requiring terminus differentiation. The principles of this sequence are better explained in Figure 1: the nonracemic compound (enriched in the *R*-enantiomer) when treated with the bifunctional nonchiral reagent as in step **a** gives three stereoisomers in the ratio expected from simple calculations.[2] If the *meso* stereoisomer can be separated by crystallization, the enantiomeric purity of the *R,R* form can be raised up to one single enantiomer in favorable conditions. The compound obtained from step **b** is a protected form of the enantiomerically enriched starting material and can be further transformed (step **c**) and finally deprotected (step d) to give the required product, allowing the recovery of the bifunctional auxiliary.

We here report the application of the former sequence using as starting materials 2,3-*O*-isopropylidene glycerol **1** as a chiral educt, the terephthaloyl group **2** as achiral linker, and the amino diol **3**, intermediate in the synthesis of optically active timolol,[7] as the synthetic target (Figure 2). We used as starting materials 2,3-*O*-isopropylidene glycerol **1** of (*S*) or (*R*)-absolute configuration[8−10] of 80% ee as resulting from uncomplete resolution of the racemic mixtures.[11] Their esters with terephthalic acid were easily and quantitatively obtained via esterification with terephthaloyl dichloride (**2a**) or methyl terephthalate (**2b**) in standard conditions. Functionalized terephthalic acids are among the least expensive bicarboxylic acid derivatives; they often give crystalline esters which are easily cleaved via basic transesterification in alcoholic medium at room temperature. They are otherwise stable in acid conditions allowing the series of manipulation successively described. Terephthalates are therefore

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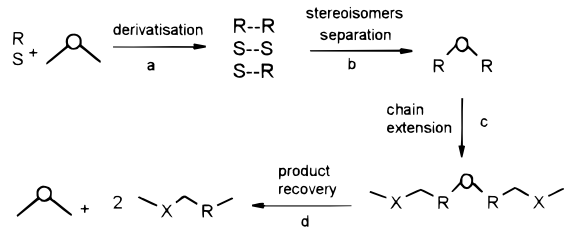

Figure 1. (a) Derivatization of a nonracemic mixture with a nonchiral bifunctional compound. (b) Separation of the major stereoisomer from the *meso* form (and eventually from the minor enantiomer) by crystallization. (c) Chain growth in the two identical directions on the protected intermediate. (d) Deprotection and product recovery.

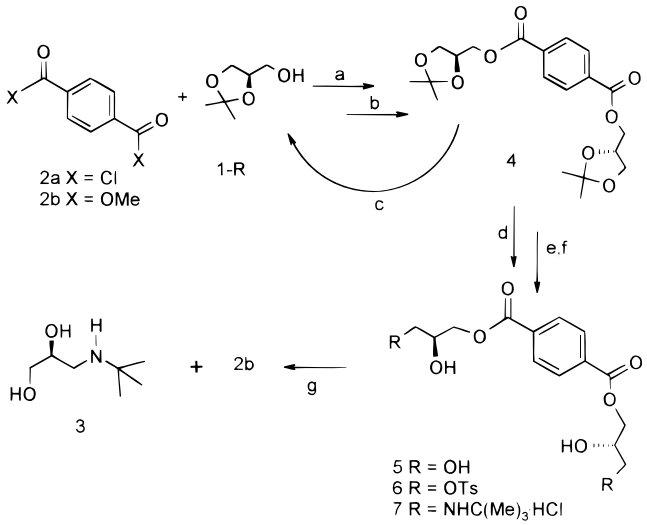

Figure 2. (−)-(*S*)-1-(*tert*-Butylamino)propane-2,3-diolhydrochloride (**3**·HCl) intermediate in the industrial synthesis of (*S*)-timolol[14] was obtained starting from (*R*)-**1** of low enantiomeric excess, in good yield and high enantiomeric excess. Other syntheses of (*S*)-timolol employ as starting material the same C3 chiral synthon **1** of (*S*) absolute configuration.

preferable in our opinion to oxalates[6] or phthalate[12] esters for the same purpose. Starting with (*R*)-2,3-*O*-isopropylidene glycerol of 80% ee we obtained the corresponding crystalline (*S*,*S*), (*R*,*R*), and (*R*,*S*) diesters in the expected[2] ratio of 81:1:18 as proven from HPLC on chiral stationary phase.

Crystallization from *n*-hexane gave the (2*S*,2′*S*)-bis-2,3-*O*-isopropylideneglycerol terephthalate freed from the *meso* diasteroisomer. After three further crystallizations, we obtained the pure enantiomer from which, after hydrolysis, enantiomerically pure (*R*)-2,3-*O*-isopropylideneglycerol was secured in 55% yield estimated on the available enantiomer in the starting mixture. The enantiomeric excess of the product was evaluated to be of >98% from HPLC on the chiral stationary phase and was confirmed by the rotation value of the isopropylideneglycerol obtained after basic hydrolysis of the ester. Thus the enrichment of the mixture was achieved with an efficiency which goes beyond the statistical ratio,[13] indicating a partial spontaneous resolution in the final crystallization. The separation from the *meso* form was particularly efficient when the mixture was seeded with crystals of the appropriate enantiomer. The pure stereoisomer was collected in one single crystallization step in 60% yield based on the available enantiomer in the mixture[13] when 5% of one single enantiomer was used for seeding. Thus starting with easily accessible compounds of low/moderate enantiomeric excess it should be possible to obtain single enantiomers in good yield by the simple derivatization/crystallization method. In our particular case, the diesters obtained can be directly used in further modification in this protected form. To this end, **4** was hydrolyzed quantitatively in the presence of a Dowex (H^+) resin to the corresponding doubly protected chiral glycerol **5**. In simple successive steps this material was transformed selectively into the primary ditosylate **6.** The latter product was the only compound in the synthesis which was not crystalline and was used as such in further transformations. Displacement of the tosylate with *tert*-butylamine was accomplished readily giving the corresponding *tert*-butylamino derivative **7** in good yields. The target amino alcohol was obtained by refluxing the diester in methanol and simple partition between solvents, in the form of the crystalline hydrochloride **3**·HCl in 45% total yield from enantiomerically pure **4** (Figure 2). The amino alcohol proved to be enantiomerically pure by comparison with data from the literature.[7]

(−)-(*S*)-1-(*tert*-Butylamino)propane-2,3-diol hydrochloride (**3**·HCl), an intermediate in the industrial synthesis of (*S*)-timolol,[14] was obtained starting from (*R*)-**1** of low enantiomeric excess, in good yield and high enantiomeric excess. Other syntheses of (*S*)-timolol employ as starting material the same C3 chiral synthon **1** of (*S*) absolute configuration.

Experimental Section

^{1}H and ^{13}C NMR spectra were run on a 250 MHz or a 300 MHz instrument with TMS as internal standard.

Chiral HPLC was performed on an apparate equipped with UV detector. The analysis was performed on a Chiralcell OD 25 cm × 4 mm, flow 0.6 mL/min, eluent *n*-hexane/2-PrOH 8/2, T = 25 °C.

(−)-(2*S*,2′*S*)-Bis-2,3-*O*-isopropylideneglycerol Terephthalate (4). (−)-(*R*)-Isopropylideneglycerol (80% ee), 25 g (0.189 mol), was dissolved with 115 mL of anhydrous CH_2Cl_2, and 15 mL of anhydrous pyridine in a 1 L round bottomed flask and 0.75 g (0.006 mol) of 4-(dimethylamino)pyridine were added. The flask was cooled with an ice bath, and 19.1 g (0.094 mol) of terephthaloyl dichloride was added in small portions under stirring in 1 h. The mixture was then allowed to reach room temperature and left under stirring overnight. The solid formed was filtered off, and the solution was washed with a cold saturated solution of $KHSO_4$ (25 mL), cold water (20 mL), a cold saturated Na_2CO_3 solution (20 mL), and cold water (25 + 25 mL). The organic phase was dried with anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure to give a white solid which proved to be analytically pure after crystallization from *n*-hexane (49 g, 87%).

For analytical purposes 2 g of the previous solid was purified by chromatography and crystallized from *n*-hexane to give a final compound of mp 79−80.5 °C: ^{1}H NMR δ ($CDCl_3$) 1.39 (s, 6H), 1.46 (s, 6H), 3.88 (q, 4H, J_{gem} = 8.5 Hz, J_{vic} = 5.4 Hz), 4.16 (q, 4H, J_{gem} = 8.5 Hz, J_{vic} = 6.18 Hz), 4.32−4.53 (m, 6H), 8.15 (s, 4H); ^{13}C NMR δ 25.35, 26.74, 65.50, 66.29, 73.57, 109.98, 129.74, 133.74, 165.5. Anal. Calcd for $C_{20}H_{26}O_8$: C, 60.90, H, 6.64. Found: C,60.84, H,6.71.

Enantiomerically Pure (−)-(2*S*,2′*S*)-Bis-2,3-*O*-isopropylideneglycerol Terephthalate (4). The crude ester obtained

(12) We were not able to obtain a crystalline diester from 2,3-*O*-isopropylideneglycerol and phthalic acid.

(13) If x is the molar fraction of the major enantiomer in the mixture, the diesters will be formed in the following ratios: x^2:(1 − x)^2:2x(1 − x) for the major enantiomer, minor enantiomer, and *meso* form, respectively. If the *meso* stereoisomer is removed from the mixture, then the ratio between the two enantiomers, which in the starting product was x:(1 − x), becomes x^2:(1 − x^2).

(14) See Chapter 9.IV in ref 1a.

from the preceding step was analyzed by HPLC using a Chiralcell OD chiral column: it was a 82:18:1 mixture of the (2*S*,2′*S*) (t_R 13.6 min), *meso* (2*S*,2′*R*) (t_R 15.8 min), and (2*R*,2′*R*) (t_R 26.8 min) stereoisomers as predicted by the statistical calculation. Then 25 g of the compound was dissolved in *n*-hexane (300 mL) at reflux. Analysis of the collected material and of the mother liquor showed that the major stereoisomer crystallizes preferentially, while the mother liquors are enriched in the *meso* compound. After three further crystallizations, the crystalline material collected (11.6 g, 55% of the available enantiomer in the starting mixture) was enantiomerically pure as judged from HPLC on the chiral stationary phase: $[\alpha]^{D}_{20}$ −8.9 (*c* 3, ethyl acetate). If the same mixture was seeded with 5% of the pure enantiomer in a slightly more diluted solution, the pure stereoisomer was obtained in one single crystallization in 60% yield.

Enantiomerically Pure (−)-(2*R*)-2,3-*O*-Isopropylideneglycerol (*R*-1). A total of 15 g of (−)-(2*S*,2′*S*)-bis-2,3-*O*-isopropylideneglycerol terephthalate (**4**) purified as previously described was dissolved in 200 mL of 10% sodium hydroxide containing 60 mL of ethanol. The mixture was refluxed for 30 min and extracted with CH_2Cl_2 (4 × 60 mL) and the solvent removed in vacuum. The residue was distilled in a bulb-to-bulb apparatus to give pure isopropylideneglycerol (6 g, 90%) with $[\alpha]^{20}_D$ −22.19 (*c* 2.5, EtOH).

(2*S*,2′*S*)-Bis-1-terephthaloyl-2,3-dihydroxypropane (5). A total of 25 g of (−)-(2*S*,2′*S*)-bis-2,3-*O*-isopropylideneglycerol terephthalate (**4**) in 70 mL of MeOH and 10 mL of water was mixed with 27 mL of Dowex 50W (H^+) resin in a 250 mL round bottomed flask, and the temperature was raised to 70 °C under vigorous stirring. The reaction was complete after about 90 min as judged from TLC analyses (CH_2Cl_2/MeOH 80:20). The resin was filtered off and rinsed with methanol, and the solvent was evaporated under reduced pressure to give an hazel brown solid. This crude product was crystallized twice with 90 mL of ethyl acetate to obtain 13.4 g (82%) of a pure solid: mp 118 °C dec; $[\alpha]^{20}_D$ +19.3 (*c* 1, MeOH); ^{1}H NMR δ 3.69 (s, 2H), 3.71 (s, 2H), 4.04 (m, 2H), 4.36 (q, 2H, J_{gem} = 11.3 Hz, J_{vic} = 6.03 Hz), 4.47 (q, 2H, J_{gem} = 11.3 Hz, J_{vic} = 4.14 Hz), 8.15 (s, 4H); ^{13}C NMR δ 64.07 , 67.55, 71.17, 130.70, 135.38, 167.06. Anal. Calcd for $C_{14}H_{18}O_8$: C, 53.50; H, 5.77. Found: C, 53.54; H, 5.76.

(2*R*,2′*R*)-Bis-1-terephthaloyl-2-hydroxy-3-(tosyloxy)propane (6). A total of 5 g (0.0159 mol) of (+)-(2*S*,2′*S*)-bis-1-terephthaloyl-2,3-dihydroxypropane (**5**) was dissolved in 30 mL of anhydrous pyridine. *p*-Toluensulfonyl chloride 6.06 g (0.0318 mol) was then added in small portions keeping the temperature around 10 °C with external cooling. The reaction was complete after 70−80 min as judged from the disappearance of the substrate (TLC analyses, CH_2Cl_2/MeOH 95:5, ditosylate R_f = 0.39). The crude reaction mixture was diluted with 70 mL of CH_2Cl_2 washed with 1.5 N HCl (3 × 100 mL) and aqueous $NaHCO_3$ to neutrality and dried with anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The dense oil obtained (9.61 g) was chromatographed with 750 mL of flash silica gel using a 65 mm diameter column. The mixture CH_2Cl_2/MeOH (100:0 to 98.5:1.5) was employed as eluent. Then 7.8 g (81%) of a clear oil was obtained $[\alpha]^{20}_D$ −3.1 (*c* 1, $CHCl_3$), identified as the ditosylate derivative: ^{1}H NMR δ 2.40 (s, 6H), 4.16 (m, 4H), 4.23 (m, 2H), 4.41 (dd, 4H, *J* = 3.32 Hz), 7.32 (d, 4H, J_{ortho} = 9.09 Hz), 7.80 (d, 4H, J_{ortho} = 9.09 Hz), 8.00 (s, 4H); ^{13}C NMR δ 21.62, 65.23, 67.65, 70.03, 127.65, 129.70, 130.04, 132.10, 133.41, 145.36, 165.50. Anal. Calcd for $C_{28}H_{30}O_{12}S_2$: C, 54.01; H, 4.86. Found: C, 53.96; H, 4.78.

(2*S*,2′*S*)-Bis-1-terephthaloyl-2-hydroxy-3-(*tert*-butylamino)propane Hydrochloride (7). A total of 5 g of the ditosylate (**6**) (0.0080 mol) was dissolved into freshly distilled *tert*-butylamine (TBA) (25 mL), and the mixture was heated at reflux for 7 h. The disappearance of substrate can be followed by TLC analyses using the mixture CH_2Cl_2/MeOH (95:5) as eluent. When the reaction was complete, the excess of TBA was evaporated in vacuum and the residue was treated with ethyl acetate to precipitate the salt between TBA and *p*-toluensulfonic acid that was filtered off. The solvent was then evaporated and the residue dissolved in anhydrous CH_2Cl_2 and treated with gaseous HCl. The precipitate was filtered and crystallized from anhydrous acetone. With this procedure 3.28 g of compound **7** as hydrochloride was obtained (80%): mp 203 °C; $[\alpha]^{20}_D$ −8.29 (*c* 1, MeOH); ^{1}H NMR δ 1.4 (s, 18H), 3.31 (dd, 2H, J_{gem} = 12.58 Hz, J_{vic} = 9.75 Hz), 3.26 (m, 2H), 4.27 (m, 2H), 4.40 (m, 4H), 8.20 (s, 4H); ^{13}C NMR δ 25.77, 45.43, 58,37, 66.81, 67.91, 130.89, 135.23, 166.77. Anal. Calcd for $C_{22}H_{38}O_6Cl_2$: C, 56.29; H, 8.16. Found: C, 56.21; H, 8.22.

(−)-(*S*)-1-(*tert*-Butylamino)propane-2,3-diol Hydrochloride (3·HCl). A total of 5 g of compound **7** was dissolved in MeOH (50 mL), and the reaction was heated to reflux for about 2 h. The progress of reaction can be followed by TLC analyses using the mixture $CHCl_3$/MeOH/NH_3 (65:30:2.5) as eluent. After the transesterification was complete, the solvent was carefully evaporated under reduced pressure to give 5.2 g of a solid compound. The crude material was dissolved in $CHCl_3$ and the solution extracted with 1.5 N HCl. The aqueous layer was separated, and the water was evaporated under reduced pressure. The dense oil was dried in vacuum over P_2O_5 for 1 day. After crystallization with acetone (20 mL), 3.63 g (84%) of a white solid was collected with mp 83−84 °C and $[\alpha]^{20}_D$ −26.01 (*c* 1, MeOH): ^{1}H NMR δ 1.40 (s, 9H), 2.93 (t, 1H, *J* = 10.47 Hz), 3.18 (d, 1H, *J* = 12.68), 3.57 (m, 2H, J_{gem} = 11.49, J_{vic} = 5.49), 3.90 (m, 1H); ^{13}C NMR δ 28.35, 45.40, 50.61, 65.77, 70.40. Anal. Calcd for $C_7H_{18}O_2NCl$: C, 45.77; H; 9.88. Found: C, 45.68; H, 9.79.

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