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# Stereoselective Preparation of Ethyl 2,3-Dihydroxy-4,4,4-trifluorobutyrates via Enzymatic Optical Resolution

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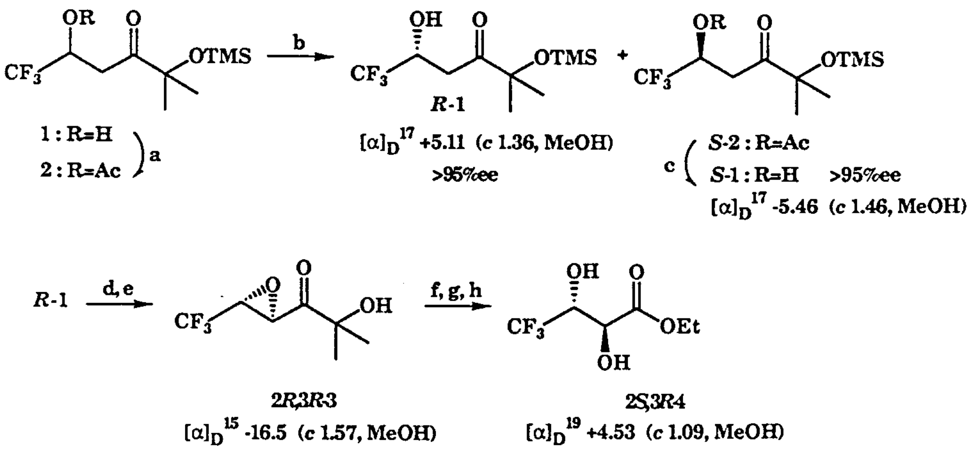
Abstract: Ethyl 2,3-dihydroxy-4,4,4-trifluorobutyrate was prepared in a highly diastereo- as well as enantioselective manner via enzymatic optical resolution followed by chemical transformations with complete retention of their configurations.

Requirements for the development of new methods for the preparation of molecules with a trifluoromethyl ($CF_3$) group in a highly stereoselective manner[1] has been rapidly increasing due to their potential and applicability as pharmaceutically active substances,[2] optically active ferroelectric devices,[3] and so on. Our previous reports[4] have clearly demonstrated the usefulness of the enzymatic optical resolution of esters with a $CF_3$ moiety, and here we would like to report the preparation of title compounds with high diastereo- as well as enantiomeric purity, which are anticipated to be utilized as building units for the construction of, for example, $CF_3$ analogs of 6-deoxysugars.

The desired ester with **4** *anti* relative stereochemistry was prepared as in Scheme I. Thus, trifluoromethylated acetate **2** was subjected to the lipase-catalyzed asymmetric hydrolysis[4a] (by lipase MY[5] from *Candida cylindracea*) to afford ***R*-1** and unreacted substrate ***S*-2**, the latter of which was further converted into the enantiomeric alcohol ***S*-1** with lipase P[5] (from *Pseudomonas fluorescens*). Their derivatization into the corresponding MTPA ester unambiguously proved >95%ee for both alcohols by $^{19}F$ NMR spectroscopy. ***R*-1** was then reacted with 2 equiv of LDA followed by the addition of iodine to produce, via iodination-intramolecular $S_N2$ displacement, the epoxide **2*R*,3*R*-3**.[1a,6] Further oxidative cleavage, ring opening, and esterification processes afforded the desired compound **2*S*,3*R*-4** in good yield without loss of optical purity. The same strategy from ***S*-1** readily realized the isolation of the enantiomeric *anti*-dihydroxybutyrate **2*R*,3*S*-4**.[6]

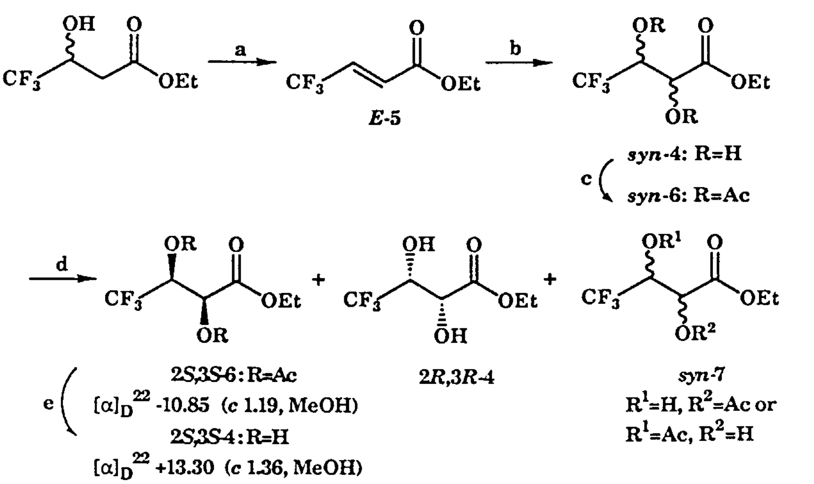
On the other hand, the *syn* isomer was synthesized in a more straightforward manner (Scheme II). Thus, ethyl 4,4,4-trifluorocrotonate ***E*-5**[6] from the corresponding β-hydroxyester was transformed by potassium permanganate into the racemic diol ***syn*-4**[6] with high stereoselectivity, which was acetylated to afford the substrate for the enzymatic optical resolution. Lipase MY was found to hydrolyze **2*R*,3*R*** isomer preferentially with concomitant formation of monoacetates ***syn*-7** and treatment of the unchanged substrate with lipase P, after the chromatographic separation, yielded **2*S*,3*S*-4** in 98% ee,[7] which was determined by $^1H$ NMR after the derivatization into alcohol **12** followed by esterification with with MTPA-Cl. At present, an effective route for **2*R*,3*R*-4** has not been found because monoacetates formed during the enzymatic process proved inseparable from the corresponding diol **2*R*,3*R*-4** while it could be realized by the search of the better matched pair of enzyme and acyl group as in previous reports.[8] The stereochemistry of the diols thus obtained was proved as follows (Scheme III). Thus, deaminohydroxylation of optically active 4,4,4-trifluorothreonine,[9] proceeded with retention at the reaction center,[10] and the comparison of the optical

Scheme I



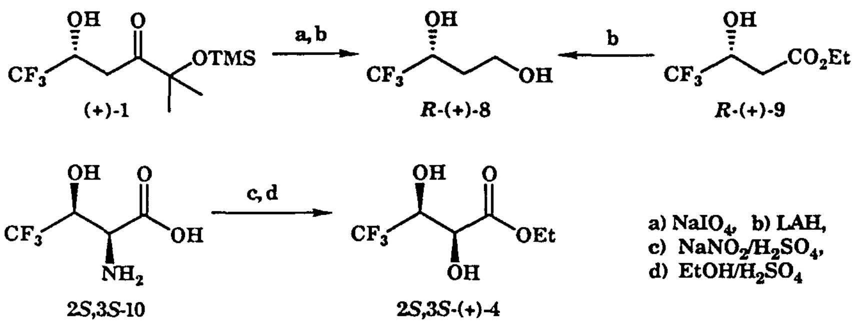

a) AcCl, pyr (97% yield), b) lipase MY (43% conversion, 27% yield for *R*-1 and 48% recovery for *S*-2), c) lipase P (82% conversion, 60% yield for *S*-1), d) LDA (2 equiv), e) $I_2$ (71% yield from *R*-1), f) $NaIO_4$, g) KOH/DMSO, h) EtOH, $H^+$ (81% yield from 2*R*,3*R*-3)

Scheme II



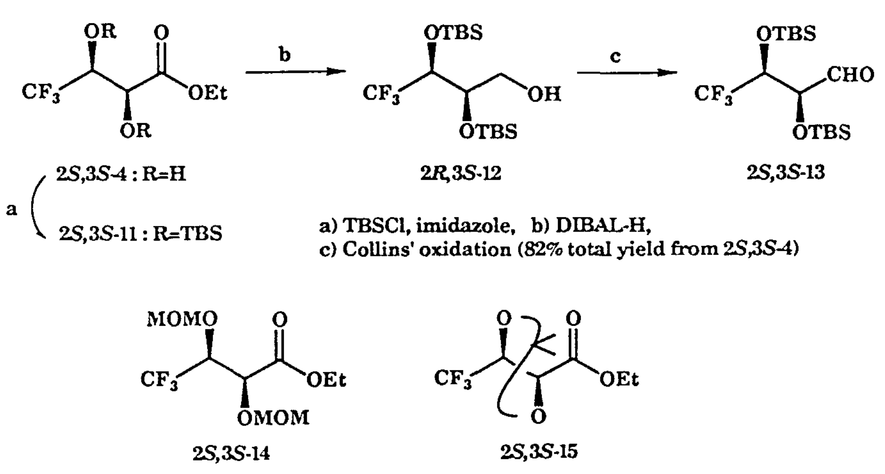

a) TsCl, $Et_3N$ (82% yield), b) $KMnO_4$ (50% yield), c) AcCl, pyr (93% yield), d) lipase MY (51% conversion, 58% combined yield for 2*R*,3*R*-4 and *syn*-7), e) lipase P (100% coversion, 26% yield for 2*S*,3*S*-4 from *syn*-6) rotation value led us to conclude that this product was completely identical with the diol ester **2*S*,3*S*-4** obtained from ***syn*-6** by two step hydrolysis. On the other hand, stereostructure of ***R*-1** was confirmed by the derivatization into the butanediol **8** followed by the comparison of the optical rotation value with the sample from β-hydroxyester possessing *R*-configuration.[4] Considering of the physical properties of the final product **2*S*,3*R*-4** along with the reaction mechanism, we reached to the conclusion that the diol ester derived from ***R*-1** possessed **2*S*,3*R*** stereochemistry.

Scheme III




As an example of the utilization of optically active 2,3-dihydroxybutyrates, the preparation of aldehyde **2*S*,3*S*-13** was investigated because this material would be expected to be a useful chiral building block on the basis of the results for the same type of compounds without fluorine atoms.[11] Elaboration of this process (Scheme IV) with three different types of protective groups such as *t*-butyldimethylsilyl (TBS, **2*S*,3*S*-11**), methoxymethyl (MOM, **2*S*,3*S*-14**), or isopropylidene (**2*S*,3*S*-15**) revealed their interesting characteristics: i) esters were found to be stable under the condition of DIBAL-H in an aprotic solvent at -78 °C, while LAH cleanly furnished the corresponding alcohols except for **2*S*,3*S*-11**,[12] ii) Swern oxidation of primary

Scheme IV



alcohols caused partial epimerization at α-position to the carbonyl group in every cases, while Collins'reagent led to the deprotection during the reaction course when **2*S*,3*S*-14** or **2*S*,3*S*-15** were employed, iii) preparation of acetonide **2*S*,3*S*-15** required a long reaction time (8 days under reflux in acetone with 10 equiv of 2,2-dimethoxypropane, 56% yield; 8 days reflux in toluene with 20 equiv of the same reagent, 78% yield) and resulted in 30 to 50% of transesterification. For obtaining the desired aldehyde, we eventually found a two-step conversion (DIBAL-H reduction and Collins' oxidation) employing the TBS-protected ester **2*S*,3*S*-11**, with complete retention of the original stereochemistry. Its diastereomer with *anti* relative stereochemistry, for example **2*S*,3*R*-4**, was also transformed by the same manner into **2*S*,3*R*-13** in 55% total yield.

In conclusion, the preparation of three stereoisomers out of the four possible isomers of dihydroxybutyrates was realized on the basis of a chemoenzymatic procedure as described above and the utilization of these compounds for diastereoselective reactions as well as the establishment of the procedure to access to the fourth isomer **2*R*,3*R*-4** are in progress in our laboratory.

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5) Lipase MY was obtained from Meito Sangyo Co., Ltd. (Japan) and lipase P was purchased from Amano Pharmaceutical Co., Ltd. (Japan).

6) Only one stereoisomer was observed by $^{1}H$, $^{13}C$, and $^{19}F$ NMR spectra.

7) Optical purity in this case was determined by $^{1}H$ NMR spectroscopy after conversion of **2*S*,3*S*-4** into the corresponding **2*R*,3*S*-12** followed by the esterification with MTPA-Cl.

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12) Many products were detected by $^{19}F$ NMR after LAH reduction of **2*S*,3*S*-11**, probably due to the TBS-migration and/or epimerization.