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Synthesis of Enantiomerically Pure (1*R*,2*S*)- and (1*S*,2*R*)-2-Amino-1,2-bis(pentafluorophenyl)ethanols

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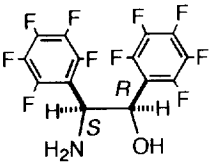
Abstract: Enantiomerically pure (1*R*,2*S*)- and (1*S*,2*R*)-2-amino-1,2-bis(pentafluorophenyl)-ethanols **1a** and **1b** have been prepared from (±)-2-(*t*-butyldimethylsiloxy)-2-(pentafluorophenyl)acetonitrile in three steps involving resolution of (±)-**1** by salt formation with *D*-camphor-10-sulfonic acid. The absolute configuration of **1a** was established by X-ray crystallographic analysis after camphorsulfonylation.

A fluorine atom introduced into a molecule varies the structural and electronic properties of the surrounding carbon skeleton and thus have been utilized frequently for enhancement of the biological activity or the molecular reactivity. We report here the synthesis of (1*R*,2*S*)-2-amino-1,2-bis(pentafluorophenyl)ethanol **1a** and its antipode (*1S,2R*)-**1b**, interesting candidates as chiral ligands, both of which have a pair of highly electron-deficient phenyl rings. The perfluorinated phenyl group has been reported to have not only an electron-withdrawing property but also a striking stacking ability with electron-rich arenes.[1] Compounds **1a** and **1b** bearing such functions are expected to endow a new fluorine-induced recognition ability as chiral ligands. The corresponding non-fluorinated analogs, (1*R*,2*S*)- and (1*S*,2*R*)-2-amino-1,2-diphenylethan-1-ols **2a** and **2b**, have been widely used in asymmetric syntheses.[2] For example, in the utilization of **2** as the oxazaborolizine catalyst, the Lewis acidity of the borane atom plays a definitive role on the reactivity. In some recent attempts, fluorines in the molecule enhance the Lewis acidity of borane,[3] tin[4] or the ligation ability of phosphorane.[5] Moreover, attractive macrocyclic dinuclear palladium complexes involving fluorinated arene have been also reported, where they capture an electron rich arene in their fluorinated electron-deficient cavity.[6] One obstacle for such investigations is the difficulty in construction of the desired fluorinated molecules. We report here the synthetic method of enantiomerically pure **1a** and **1b** to enable to study of the physical properties and reactivity in asymmetric synthesis.

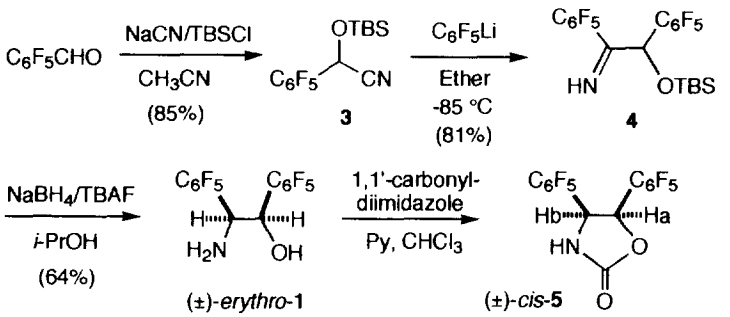


(-)-(1*R*, 2*S*)-**1a**

(±)-*Erythro*-**1** was synthesized stereoselectively in three steps from pentafluorobenzaldehyde as shown in Scheme 1. Thus, the aldehyde was converted into (±)-2-(*t*-butyldimethylsiloxy)-2-(pentafluorophenyl)-acetonitrile (**3**)[7,8] (NaCN, TBS-Cl, $ZnBr_2$ in CH_3CN) (85% yield), which was then allowed to react with pentafluorophenyllithium[9] [bromopentafluorobenzene, 1 eq. molar *n*-BuLi in ether] at -85 °C for 5 min, giving 2-(*t*-butyldimethylsilyloxy)-1-imino-1,2-bis(pentafluorophenyl)ethane (**4**) (81% yield) after purification

by flush chromatography (hexane-EtOAc, 20:1-5:1). It was used immediately for the subsequent reduction, because **4** was found to isomerize gradually to its enamine form on standing at room temperature.

Scheme 1

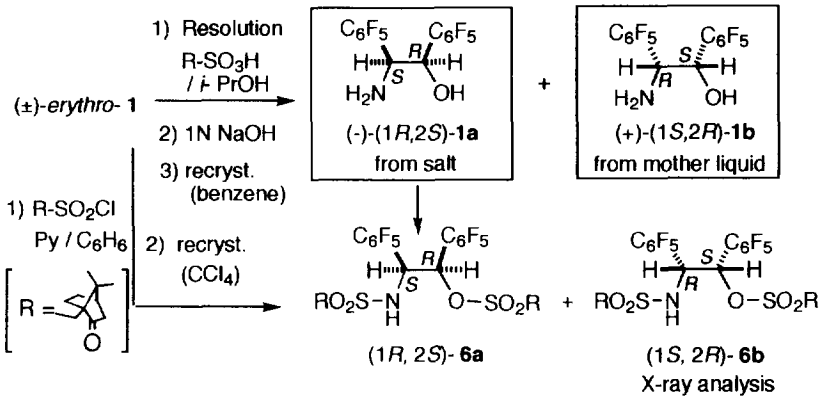


The reduction of imine **4** to amine (±)-**1** was found to be very slow compared to the corresponding non-fluorinated analog, which was reported to be readily reduced with $NaBH_4$.[10] All attempts by the conventional methods with $NaBH_4$-Lewis acids,[11] $NaBH_3CN$,[12] Pd/C/H_2,[13] Zn/AcOH,[14] and Na/EtOH[15] resulted in recovery of **4** with unidentified products. Removal of the bulky TBS group from **4** with tetrabutylammonium fluoride (TBAF) before reduction turned the reaction mixture immediately dark in color to form a complex mixture. Finally, *in-situ* generation of the alcohol from **4** and simultaneous reduction of the imine moiety were examined: a THF solution of TBAF (1.1 equiv.) was added to a cooled (0 °C) mixture of **4** (1 equiv.) and $NaBH_4$ (1 equiv.) in *i*-PrOH under nitrogen. The reaction after 1.5 h at 0 °C afforded successfully (±)-*erythro*-**1** with a single isomer (64%), which could be purified by sublimation (150 °C, 0.38 mmHg) to give a white crystal (mp 157-158 °C). These results suggest that the reason of the resistance in the reduction of the imine is not only due to the hindrance by the TBS group but also due to the repulsion between the hydride and the fluorine of C_6F_5 groups.

The erythro configuration of **1** was determined by correlation to the corresponding (±)-*cis*-oxazolidone **5**[16] by the reaction with 1,1'-carbonyldiimidazole in chloroform. ^{1}H NMR (500 MHz) analysis showed that 13% of NOE enhancement of the signal at δ 5.74 ppm due to CHb-N was exhibited by irradiation at δ 6.32 ppm due to CHa-O.

Amino alcohol (±)-*erythro*-**1** was then resolved by formation of the salt with 1.1 equiv. of *D*-camphor-10-sulfonic acid in *i*-PrOH (Scheme 2). The salt was precipitated on standing for 6 h at room temperature and the isolated salt was treated with 1N NaOH to liberate optically active (-)-(*1R,2S*)-2-amino-1,2-bis(pentafluorophenyl)ethanol (**1a**) (90% ee by the MTPA ester), which was recrystallized three times from benzene to afford enantiomerically pure **1a**[17] (40% yield on the basis of the enantiomer) as a white crystal [mp 181 °C, $[\alpha]_D^{23}$ = -20.8 (*c* 0.106, EtOH)]. The optical purity was checked by ^{1}H NMR analysis of the corresponding MTPA ester. From the supernatant, enantiomerically pure antipode (+)-(*1S,2R*)-**1b** (35% yield) [mp 181-182 °C, $[\alpha]_D^{23}$ = +19.8 (*c* 0.125, EtOH)] was also obtained after analogous recrystallization.

Scheme 2



In order to determine the absolute configuration of **1a** and **1b**, (±)-*erythro*-**1** was allowed to react with *D*-camphor-10-sulfonyl chloride/pyridine in benzene to yield a mixture of disulfonates (1*R*,2*S*)-**6a** and (1*S*,2*R*)-**6b** (79% yield), which could be also resolved by recrystallization from benzene. The firstly precipitated **6b** [mp 200–201 °C, $[\alpha]_D^{25}$ = +27.2 (*c* 0.2, $CHCl_3$)] was purified by recrystallization from CCl_4, instead of benzene, which gave a suitable crystal for X-ray analysis to determine (1*S*,2*R*)-configuration as shown in Figure 1. The crystal obtained from the supernatant was thus assigned to be (1*R*,2*S*)-**6a**. Finally, the absolute configuration of (1*R*,2*S*)-**1a** was determined by correlation to (1*R*,2*S*)-**6a** after camphorsulfonylation.

Enantiomerically pure amino alcohols (-)-(1*R*,2*S*)-**1a** and (+)-(1*S*,2*R*)-**1b** are now available and can be tested as chiral ligands.[18]

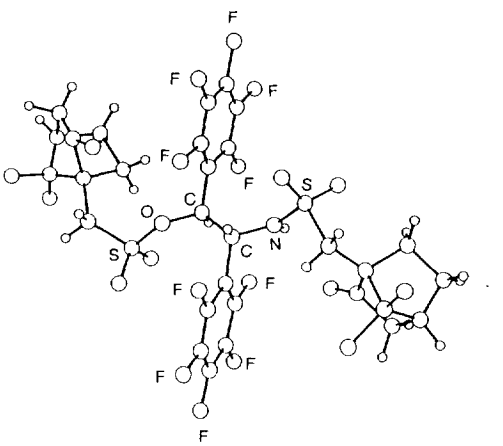


Figure 1. X-Ray diffraction structure of compound **6b**.

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17. (±)-*Erythro*-**1** (1.00 g, 2.54 mmol) and *D*-camphor-10-sulfonic acid (0.65g, 2.79 mmol) were dissolved in 5 ml of *i*-PrOH and the solution was allowed to stand for 6 h at room temperature. White precipitates were gradually formed and collected by decantation. The residual salts were then stirred in 5 ml of 1N NaOH for 30 min and the liberated **1a** was extracted with ethyl acetate. The recoverd enantiomerically enriched **1a** (90% ee by the MTPA ester) was recrystallized from 5 ml of benzene three times to give 0.20 g (40% yield on the basis of the enantiomer) of enantiomerically pure (-)-(1*R*,2*S*)-**1a**. From the supernatant, enantiomerically pure (+)-(1*S*,2*R*)-**1b** (35% yield) was obtained in a similar way. (-)-(1*R*,2*S*)-**1a**: IR (nujor) 3600-3100, 3384, 3316 cm^{-1}; ^{1}H NMR (200 MHz, δ, $CDCl_3$) 1.5-1.9 (br s, 1H, OH), 2.4-3.1 (br s, 2H, NH_2), 4.67 (d, 1H, J = 9.6 Hz), 5.25 (d, 1H, J = 9.6 Hz); ^{19}F NMR (188 MHz, δ, $CDCl_3$) 0.33-0.77 (m, 4F), 7.38 (t, 1F, J = 20.3 Hz), 8.41 (t, 1F, J = 20.3 Hz), 17.96 (dd, 2F, J = 7.20 and 21.7 Hz), 18.98 (dd, 2F, J = 7.20 and 21.7 Hz). Acceptable analytical data were obtained.
18. Expected catalytic activity has been demonstrated and the utilities are now under the active investigation.

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