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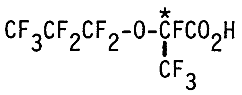
OPTICALLY ACTIVE DI(PERFLUORO-2-PROPOXYPROPIONYL)METHANE: A NOVEL LEGAND FOR NMR SHIFT REAGENT

Hajimu KAWA, Fumihiko YAMAGUCHI, and Nobuo ISHIKAWA*
Department of Chemical Technology, Tokyo Institute of Technology,
Ookayama, Meguro-ku, Tokyo 152

(+)-Di(perfluoro-2-propoxypropionyl)methane, (+)-4, an optically active β-diketone, was prepared in a good yield from (+)-perfluoro-2-propoxypropionic acid. The europium chelate of (+)-4 was found to be a very effective and useful NMR shift reagent for the direct determination of the enantiomeric composition of chiral compounds.

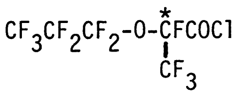
The usefulness of optically active NMR lanthanide shift reagents has been well recognized, as these reagents give a versatile method for direct determination of enantiomeric compositions.[1,2] A number of chiral or achiral β-diketones were synthesized and the utility of their lanthanide chelates was discussed.[3,4] The results reveal that lanthanide chelates with optical high stability, acidity and solubilities are especially useful, and those chelates carrying bulky and partially fluorinated ligands have been examined. From these points of view, we intended to prepare a new β-diketone ligand which has bulky perfluoro groups with a chiral center.

In our previous paper,[8] we reported a synthetic method for optically active perfluoro-2-propoxypropionic acid 1, which was regarded as a building block for our purpose.



$CF_3CF_2CF_2\text{-}O\text{-}\underset{CF_3}{\overset{*}{C}}FCO_2H$

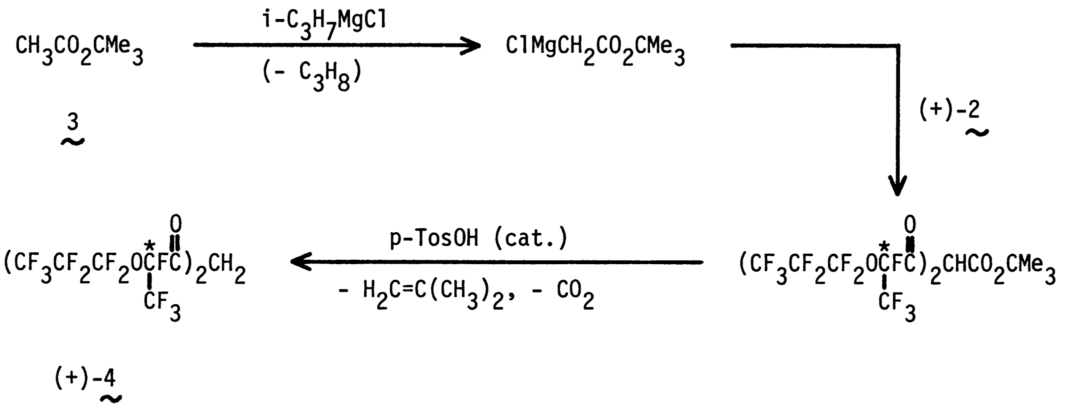
1



$CF_3CF_2CF_2\text{-}O\text{-}\underset{CF_3}{\overset{*}{C}}FCOCl$

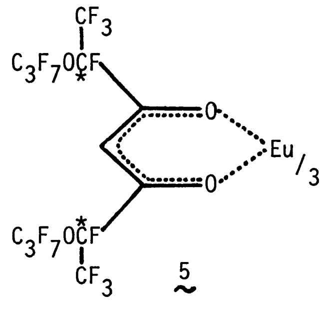
2

Meanwhile, the enolate anion from the tert-butyl acetate 3 is known to be a useful reagent for preparing β-diketone from a carboxylic acid halide, and by using this reagent a new chiral diketone (+)-4 was prepared in a good yield according to the following scheme.



For example, into a solution of isopropylmagnesium chloride (40 mmol), prepared in diethyl ether (20 ml), tert-butyl acetate (4.64 g, 40 mmol) was added dropwise at room temperature. Evolution of propane gas was observed and the solvent started gentle reflux. After stirring for 1 h, (+)-2 (6.54 g, 18 mmol), prepared from (+)-1 [α_D^{28} +25.17 ° (neat, l = 1), 95%ee[7]] and phosphorus pentachloride, was added at reflux. The mixture was stirred for 15 min at room temperature, cooled in an ice bath, and quenched with aqueous hydrochloric acid. The organic layer was separated and dried over magnesium sulfate. The solvent and excess tert-butyl acetate were removed, a catalytic amount of p-toluenesulfonic acid was added, and the mixture was heated at 120 °C for 15 min. The residual product was distilled to give (+)-4 (5.20 g, 90%), bp 94 - 96 °C/110 mmHg. α_D^{28} +34.88 ° (neat, l = 1). IR (film): 1600 cm^{-1} (C=O). ^1H NMR (CCl_4): 13.67, 5.97 ppm. ^{19}F NMR (CCl_4): δ 1.65 (1F), 4.00 (3F), 4.77 (3F), 6.55 (1F), 51.73 (2F), 57.50 (1F) ppm upfield from ext. CF_3CO_2H. Cu chelate: mp 71 - 72 °C.

The polyfluorinated β-diketone (+)-4 thus obtained was examined as a chiral lanthanide shift reagent. The europium chelate (+)-5 was prepared after the method of Goering et al.[8] as follows:



Europium(III) chloride hexahydrate (99.9%, Wako Pure Chemical Ind. Ltd.)(0.73 g, 2.0 mmol) was dissolved in ethanol (7 ml) and was added to the solution of (+)-4 (3.84 g, 6.0 mmol) in a 50% ethanolic solution (6 ml) of 1N sodium hydroxide. The mixture was stirred for 2 h, then water (10 ml) was added, and the separated oil was taken up in pentane. The pentane extract was washed with water, dried over $MgSO_4$. Evaporation of the solvent at 90 °C (0.8 mmHg) for several hours gave a fine yellow oily product. No further purification was successful despite of various attempts. However, the IR and NMR spectra of this liquid supported the structure of 5 (3.22 g, 78%). IR (film): 1630 (C=O), 1530 (C=C) cm^{-1}. ^1H NMR ($CF_2ClCFCl_2$): 3.33 ppm (broad). ^{19}F NMR ($CF_2ClCFCl_2$): δ 6.90 (6F), 7.57 (2F), 54.47 (2F), 61.83 (1F) ppm upfield from ext. CF_3CO_2H (all resonances are broad). $[\alpha]_D^{26}$ +48.52 °(c 0.67, $CF_2ClCFCl_2$).

The europium chelate 5 was very effective as an NMR shift reagent. Fig.1 shows the NMR spectra of partially resolved 1-phenylethylamine in CCl_4, in the absence and presence of (+)-5. The reagent (+)-5 induced downfield shifts as was expected and separated the α-methyl resonance into two peaks. Thus, signals for each enantiomer in the 1-phenylethylamine were clearly distinguished from each other and their relative signal intensities could be integrated. The optical purity of this sample was determined by the NMR analysis to be 30.3%, in satisfactory agreement with that determined by polarimetry (28.8%). Only a small amount of (+)-5 (reagent substrate molar ratio : r/s = 0.11, Fig. 1d) was necessary enough to obtain the satisfactory $\Delta\Delta\delta$ value (magnitude of enantiomeric shift difference) 0.20 ppm, while well known tris-(3-heptafluorobutyryl-d-camphorato) europium(III), $Eu(hfbc)_3$, needs an r/s value within the range of 0.40 to 0.60 to obtain the $\Delta\Delta\delta$ value 0.17 ppm.8) In addition, since there are no hydrogen atoms overlapping with those in the substrate, the ^1H NMR spectra are very clear as shown in Fig. 1. This seems to be the most advantageous point of our reagent to the other partially fluorinated ones. Further, this reagent is soluble in non-polar organic solvents such as carbon tetrachloride, and, in particular, is miscible with 1,1,2-trichlorotrifluoroethane (F-113). This is another feature of this reagent, as it makes micro-volume addition of (+)-5 in F-113 easy, which is of practical use for NMR analysis. Therefore, our reagent would be suitable for the complicated chiral compounds as well as relatively simple ones. Further applications are now under way.

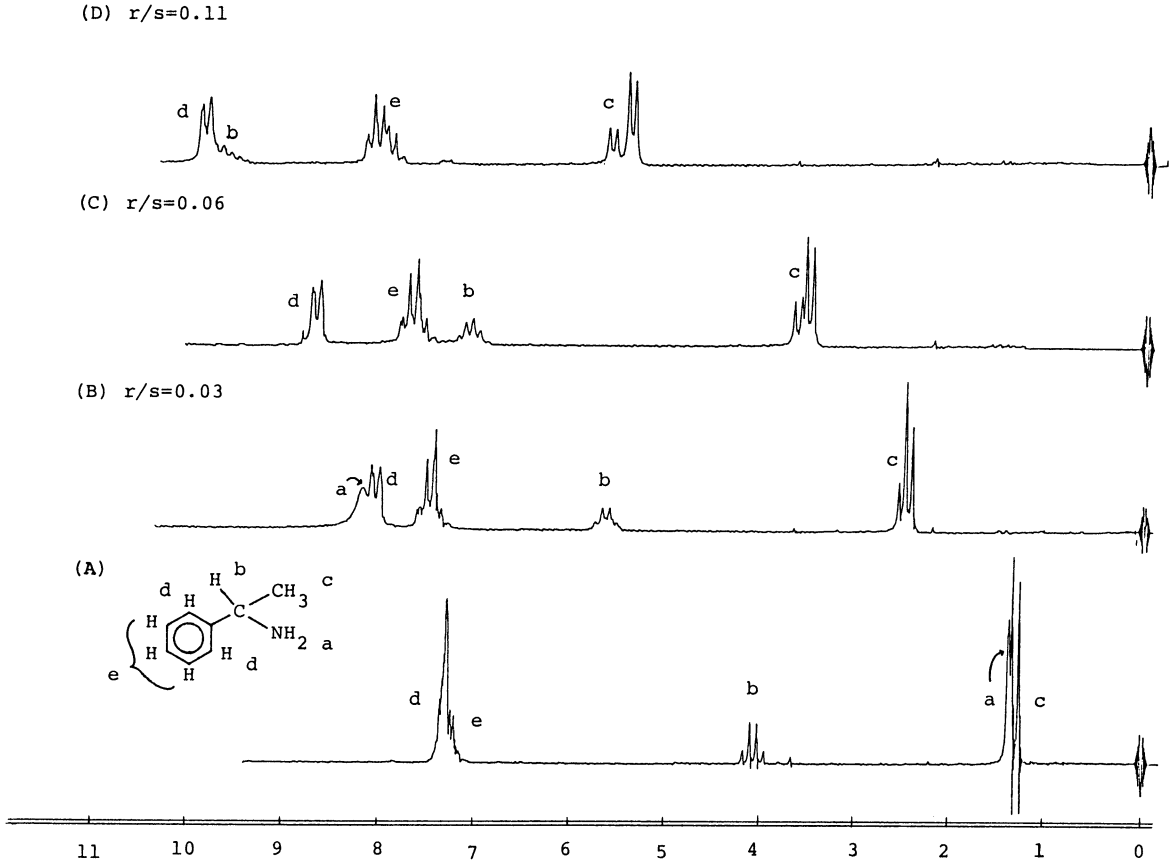


Fig. 1 ^{1}H NMR spectra for (-)rich-1-phenylethylamine in CCl_4 in the absence (A) and presence (B)∼(D) of (+)-**5** at three different (+)-**5**/substrate molar ratios (r/s).

References

1) K. A. Kime and R. E. Sievers, Aldrichimica Acta, 10, 54 (1977).

2) Y. Kosugi, Kagaku no Ryoiki, 35, 68 (1981).

3) M. F. Richardson and R. E. Sievers, Inorg. Chem., 10, 498 (1971).

4) B. Feibush, M. F. Richardson, R. E. Sievers and C. S. Springer, Jr., J. Am. Chem. Soc., 94 6717 (1972).

5) H. Kawa and N. Ishikawa, Chem. Lett., 1980, 843.

6) J. E. Dubois, S. Molnarfi, F. Henneguin, M. H. Durand and R. Fellous, Bull. Soc. Chim. Fr., 1491 (1963).

7) H. Kawa, F. Yamaguchi and N. Ishikawa, J. Fluorine Chem., submitted for publication.

8) H. L. Goering, J. N. Eikenberry, G. S. Koermer and C. J. Lattimer, J. Am. Chem. Soc., 96, 1493 (1974).

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