Tetrahedron: Asymmetry Vol. 2, No. 11, pp. 1105-1106, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

A NEW ENTRY TO HOMOCHIRAL DIFLUORINATED COMPOUNDS

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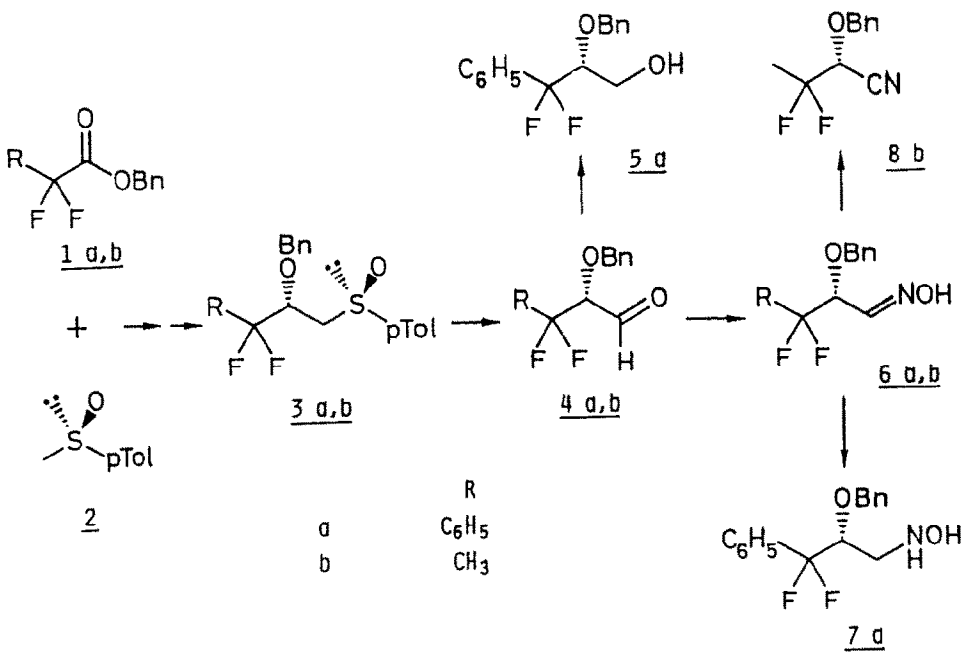
(*Received* 1 *October* 1991)

Abstract: Some homochiral compounds containing a difluoromethylene unit along with oxygen and nitrogen functionalities have been obtained starting from α,α-difluorocarboxylic esters and (+)-(R)-methyl p-tolyl sulfoxide.

The selective introduction of a difluoromethylene unit into a chiral molecule allows to obtain useful biological and pharmacological properties (e.g. transition-state analogue enzyme inhibitors, mechanism-based enzyme inhybitors...).[1] The unique general "chiron approach" for the asymmetric synthesis of geminal difluorinated compounds is the Reformatzky reaction of ethyl bromodifluoroacetate on chiral aldehydes.[2]



Here we report a new general approach to homochiral polyfunctional compounds containing the difluoromethylene unit. The easily available α,α-difluorocarboxylic esters are the source of the fluorinated part of the molecule and an optically pure sulfinyl residue is the source of chirality.

Specifically, the lithium derivative of optically pure (+)-(R)-methyl p-tolyl sulfoxide **2** was acylated with the α,α-difluorocarboxylic esters **1a,b** to afford 3,3-difluoro-1-sulfinyl-alkan-2-ones (mixture of the keto and hydrated forms).[3] Reduction of these ketones with diisobutylaluminum hydride (THF/-78 °C) after dehydration with molecular sieves (4Å) afforded corresponding $(2S,R_S)$-3,3-difluoro-1-sulfinyl-alkan-2-ols with complete diastereoselection.[4] Benzylation of the so formed hydroxyl group under standard conditions gave $(2S,R_S)$-2-benzyloxy-3,3-difluoro-1-[(4-methylphenyl)sulfinyl]alkanes **3a,b** in good overall yields (>70% from 1).

These derivatives were the key-intermediates for the synthesis of sulfur-free and homochiral difluoro compounds **4 - 8**. The Pummerer rearrangement of the sulfoxide group of **3a,b** (trifluoroacetic anhydride/2,4,6-trimethylpyridine/acetonitrile) followed by *in situ* hydrolyses of the geminal trifluoroacetyloxy-tolylthio intermediates (mercury(II) chloride/water) gave (R)-2-benzyloxy-3,3-difluoroaldehydes **4a,b**. Monoprotected difluorodiol (R)-**5a** was obtained through reduction of **4a** (sodium borohydride).

Nitrogen substituted difluorinated products have been synthetized *via* oximes (R)-**6a,b** which have been prepared from crude aldehydes **4a,b** (hydroxylamine/acetic acid/ethanol). Reduction of (R)-**6a** (sodium cyanoborohydride/methanol/pH=3) gave (R)-N-alkyl-hydroxylamine **7a** (80% yield) and dehydration (trifluoromethansulfonic anhydride/triethylamine/methylene chloride) of (R)-**6b** afforded (R)-2-benzyloxy-3,3-difluorobutyronitrile **8b** (63% yield).

The procedure here described allows to prepare also the enantiomers of the products reported above as also (-)-(S)-**2** is an easily available starting material.

Acknowledgements. Financial support by C.N.R. - Progetto Finalizzato Chimica Fine II is gratefully acknowledged.

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