Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 6, pp. 1015-1018, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $7.00+0.00

0957-4166(94)00131-6

Stereoselective synthesis of 14,14-difluorocoriolic acid

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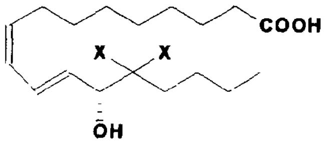
Abstract: An efficient, stereoselective synthesis of (R)-14,14-difluoro-13-hydroxy-9(Z),11(E)-octadecadienoic acid ((R)-14,14-difluorocoriolic acid) 2 starting from D-glyceraldehyde acetonide *via* the key intermediate (R)-3,3-difluoro-1,2-dihydroxyheptane 9 is reported.

Various lipoxygenase metabolites of linoleic acid have been isolated from biological systems. Among them corioloc acid 1, which was isolated from rice, acts as self-defense substance against rice blast disease [1]. Furthermore, this product is present in heart mitochondria [2] as well as in the sera of patients with familial Mediterranean fever [3] and possesses cation-specific ionophoric activity. In addition 1 has been shown to exhibit physiological properties which indicate that it plays a significant role in controlling thrombosis [4].

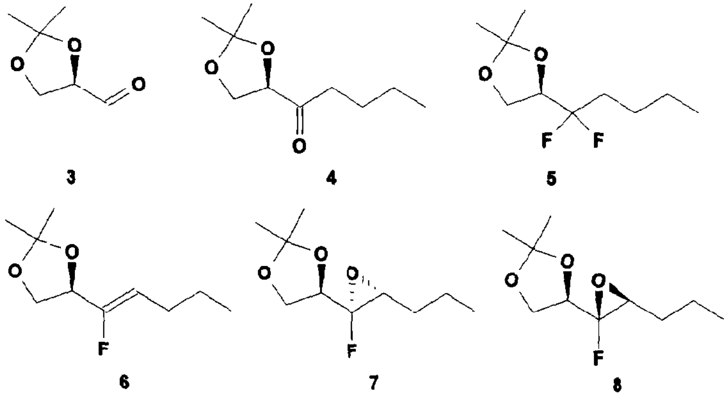


1. X = H

2. X = F

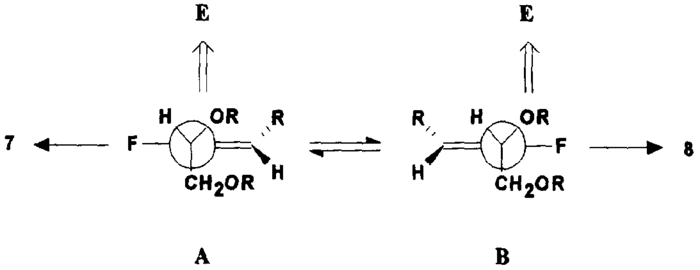
Based upon these observations we considered (*R*)-14,14-difluorocoriolic acid 2 to be an attractive target for the synthesis, since analogue 2, having C-13 hydroxyl group whose polarity is increased by virtue of the strong electron withdrawal effect of fluorine atom, may show enhanced biological activity.

We report here the synthesis of 2 starting from readily available D-glyceraldehyde acetonide 3. The reaction of 3 with butylmagnesium bromide carried out in THF at 0°C, followed by Swern oxidation afforded ketone 4[5] in 70 % yield (scheme 1). Treatment of 4 with diethylaminosulfur trifluoride (DAST) in CH_2Cl_2 gave a mixture of two products. Corresponding *gem*-difluoride 5 and elimination reaction product 6 were observed by ^{19}F NMR analysis of the reaction mixture in a ratio 5:1. In the NMR ^{19}F spectrum difluoride 5 exhibited two doublets of multiplets at -109.2 ppm and at -114.9 ppm, while (*Z*)-fluoroolefine 6 exhibited doublet of doublets at -128 5 ppm with J= 36.7 and 17.9 Hz. When the reaction was carried out in diglyme, the ratio of 5 to 6 was nearly 1.1. Two products of the reaction could not be separated. That is why the mixture was treated with mCPBA in CH_2Cl_2 (20° C, 6 h) to produce difluoride 5 and diastereomeric fluoro epoxides 7 and 8, which were easily separated by column chromatography on silica gel. The isolated yields of products were 70 % of 5[6], 10% of 7 and 4% of 8 based on 4.



Scheme 1.

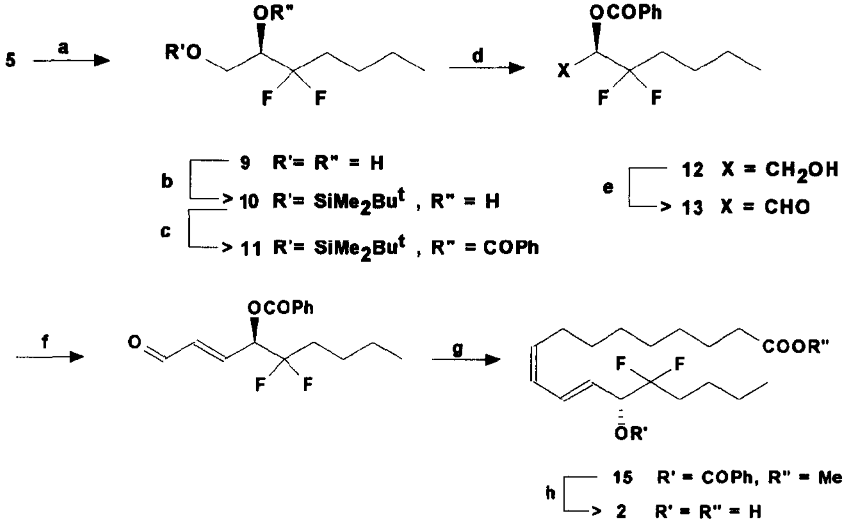
The major and minor products from the reaction of (Z)-fluoroolefine 6 with mCPBA are predicted according to transition state models A and B (Scheme 2).



Scheme 2.

It is generally agreed that the approaching electrophile is directed antiperiplanar to the perpendicularly disposed largest substituent [7,8]. According to Houk [7] from both steric and electronic reasons, the major product arises from transition state in which the donating alkyl substituent being in the *anti* position (orthogonal to the C=C double bond), the alkoxy group occupies the region close to the double bond (inside position) and the hydrogen atom occupies the outside position. The minor product comes from a transition state in which the location of the alkoxy group and hydrogen atom are reversed.

After the preparation of required precursor 5 we synthesized (*R*)-14,14-difluorocoriolic acid as follows (scheme 3). Hydrolysis of acetonide protection in 5 by 4N HCl in THF at room temperature gave 1,2-diol 9. Protection of primary alcohol of 9 with *tert*-butyldimethylsilyl chloride and 4-dimethylaminopyridine (DMAP) yielded **10**, then protection of the remaining secondary alcohol **10** with benzoyl chloride and pyridine led to **11**. Deprotection of silyl group of **11** with dioxane-H_2O-conc.HCl (100:2:5) gave **12**. Oxidation of alcohol **12** with pyridinium chlorocromate in the presence of molecular sieves 4A in dry CH_2Cl_2 led to aldehyde **13**[9] with 55% overall yield from acetonide **5**. α-Alkoxy aldehydes are known to have a marked proclivity for becoming hydrated[10,11] and so crude aldehyde **13** without any purification was homologated with (formylmethylene)-triphenylphosphorane to α,β-unsaturated aldehyde **14**[12]. At this stage the remaining part of the carbon sceleton was introduced by the condensation of **14** with the ylide, generated from 8-methoxycarbonyloctyl triphenylphosphonium bromide. The benzoate ester **15** was obtained with 72 % yield (E,Z stereoisomeric purity 96% by RP-HPLC, column Separon SIX CN, 5 μm (300 x 3.3 mm I.D.), mobile phase 0.3% of isopropanol in heptane). Alkaline hydrolysis of benzoate ester **15** yielded target 14,14-difluorocoriolic acid **2**[13].



(a) 4N HCl - THF (1:4), 20°C, 12 h, 78%; (b) *tert*-$BuMe_2SiCl$, DMAP, CH_2Cl_2, 20°C, 16 h, 82%; (c) PhCOCl, Py, CH_2Cl_2, 20°C, 16 h, 84%; (d) dioxane-H_2O-HClconc (100:2:5), 20°C, 20 h, 91%; (e) $C_5H_5NH^+ClCrO_3^-$, 4A molecular sieves, CH_2Cl_2, 20°C, 2 h, 90%; (f) $Ph_3P{=}CHCHO$, C_6H_6, reflux, 1 h, 80%; (g) $Ph_3P{=}CH(CH_2)_7COOCH_3$, -78°C to 0°C, 1 h, 85%; (h) LiOH, THF-H_2O (4:1), 20°C, 60 h, 45%.

Scheme 3

References and Notes

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5. All new compounds gave correct spectral and analytical data.
6. Purity 97% (by GLC); $[\alpha]_D$ + 4.0 (c 1.2, $CHCl_3$); ^{19}F NMR ($CDCl_3$) δ −109.2 dt (J=251 and 21 Hz, 1F), -114.9 dtd (J=251, 16.4 and 16.4 Hz, 1F); ^{1}H NMR ($CDCl_3$) δ 0.93 t (J=7.2 Hz, 3H), 1.32 - 1.47 m (10H), 1.82 - 1.99 m (2H), 4.06-4.26 m (3H).
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9. ^{19}F NMR ($CDCl_3$): δ -103.93 m; ^{1}H NMR ($CDCl_3$) δ 0.92 t (J=7.0 Hz, 3H), 1.28 - 1.63 m (4H), 1.90 - 2.18 m (2H), 5.56 dd (J=12.9 and 11.8 Hz), 7.4 - 7.7 m (3H), 8.11 m (2H), 9.75 t (J=1,5 Hz, 1H)
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12. $[\alpha]_D$ +134.3 (c 1.7, $CHCl_3$); ^{19}F NMR ($CDCl_3$) δ -106.4 dtd (J=255, 18.5 and 7.5 Hz, 1F), -108.2 ddt (J=255, 17.5 and 15.5 Hz, 1F); ^{1}H NMR ($CDCl_3$) δ 0.91 t (J=7.4 Hz, 3H), 1.26 - 1.63 m (4H), 1.90 - 2.18 m (2H), 5.99 m (1H), 6.39 ddd (J=15.5, 7.5 and 1.8 Hz, 1H), 6.91 dd (J=15.5 and 4.8 Hz, 1H), 7.4 - 7.7 m (3H), 8.10 m (2H), 9.64 d (J=7.7 Hz, 1H).
13. ^{19}F NMR ($CDCl_3$) δ -110.3 dm (J=247 Hz, 1F), -112.3 dm (J=247 Hz, 1F); ^{1}H NMR ($CDCl_3$) δ 0.92 t (J=6.9 Hz, 3H), 1.25 - 1.65 m (15H), 1.85 - 2.02 m (2H), 2.18 m (2H), 2.35 t (J=7.5 Hz, 2H), 4.33 m (1H), 5.52 dt (J=11.0 and 7.4 Hz, 1H), 5.69 dd (J=15.1 and 6.3 Hz, 1H), 6.02 dd (J=11.0 and 11.0 Hz, 1H), 6.70 dd (J=15.1 and 11.0 Hz, 1H).

(*Received* 30 *March* 1994)