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Biocatalyzed synthesis of both enantiopure fluoromisonidazole antipodes

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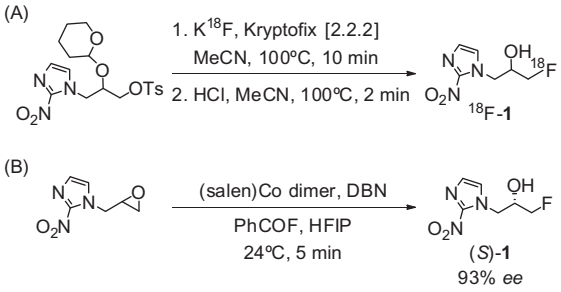
ABSTRACT

Fluoromisonidazole (FMISO or F-MISO) is a radiotracer for positron emission tomography when ^{18}F-labeled and is administrated in its racemic form. Herein, a straightforward synthesis of both enantiopure antipodes is proposed through a one-pot two-step microwave protocol to obtain a fluorinated ketone precursor followed by bioreduction using alcohol dehydrogenases from *Rhodococcus ruber* (ADH-A) or *Lactobacillus brevis* (LBADH).

The relevance of chiral fluorohydrins has been highlighted with the recent development of novel methodologies based on, for example, the use of transition metal catalysis applied to nucleophilic or electrophilic fluorination,[1] through the aperture of epoxides,[2] or the reduction of the corresponding ketones.[3] These compounds are very interesting precursors for agrochemicals and pharmaceuticals,[4] and they also present a remarkable role as liquid crystals,[5] and as radiotracers when they are ^{18}F-labeled for positron emission tomography (PET).[6]

In particular, fluoromisonidazole (FMISO or F-MISO), 1-(2-nitroimidazol-1-yl)-3-fluoropropan-2-ol (**1**, Scheme 1), is a derivative of the nitroimidazole group of compounds which have widely been investigated as hypoxic cell sensitizers. ^{18}F-Labeled derivative of F-MISO has extensively been used to image hypoxic tissues in vivo with PET technology and also to predict cancer recurrence in living cells.[7]

Since this compound presents a chiral center at position 2, it is administrated in its racemic form although it is well-known that the biological activity of a racemate can largely differ from each enantiomer.[8] Among the different methodologies described to obtain this derivative, it can be highlighted the synthesis through fluoride displacement of a primary tosylated alcohol, and subsequent deprotection of the tetrahydropyranyl protecting group from the secondary alcohol under acidic conditions (Scheme 1A).[9] Very recently it has been proposed the first asymmetric synthesis of



Scheme 1. Previous synthesis of: (A) racemic labeled, and (B) enantioenriched unlabeled F-MISO.

(*S*)-**1** via enantioselective aperture of an epoxide precursor with 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), 5-diazabicyclo[4.3.0]non-5-ene (DBN), benzoyl fluoride, and a linked (salen)Co catalyst to achieve the kinetic resolution with 93% ee and 40% yield (Scheme 1B).[10]

Due to the short half-life of ^{18}F-labeled F-MISO, it would be highly desirable to find a methodology that could easily afford both stable unlabeled F-MISO antipodes, so the different biological properties of each enantiomer could be more easily assessed. To achieve this goal, here we propose the synthesis of a fluorinated ketone precursor (**5**, Scheme 2) that could be selectively reduced employing stereocomplementary alcohol dehydrogenases (ADHs),[11] enzymes able to achieve the selective reduction of carbonyl compounds or the oxidation of alcohol derivatives under

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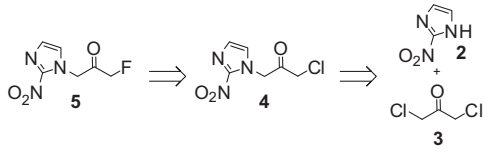


Scheme 2. Proposed retrosynthesis to obtain fluorinated ketone **5**.

mild hydrogen transfer reaction conditions in aqueous medium. Starting from this prochiral ketone, this methodology could afford the final enantiopure fluorohydrin in a theoretical yield of 100%.

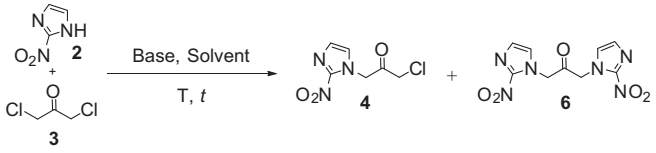
Therefore, in order to obtain ketone **5**, the straightforward synthesis shown in Scheme 2 was envisaged. Starting from commercially available 2-nitroimidazole **2** and 1,3-dichloroacetone **3**, the chlorinated ketone **4** could be synthesized through nucleophilic substitution, which would afford desired ketone **5** using a fluoride source.

In a first set of experiments, different ratios of compounds **2** and **3** were treated with several solvents and bases under various temperatures to synthesize ketone **4**, although it was noticed that in many cases disubstituted derivative **6** was also obtained as a by-product (Table 1). Thus, using an equimolar ratio between compounds **2** and **3** to minimize the formation of **6**, dichloromethane (entry 1), acetone (entries 2 and 3), and acetonitrile (entries 4 and 5) were employed at different temperatures in the presence of sodium carbonate as the base, observing that while for the first solvent no reaction occurred, probably due to the low solubility of the base, better results were achieved with the other two solvents, although undesired ketone **6** (14–30%) was obtained as a by-product. Since the use of acetonitrile allows higher reaction temperatures, we further studied more conditions with this organic solvent. When the process was performed under reflux (entries 6 and 7), the employment of 3 equiv of the base helped to achieve a higher conversion of ketone **4** (57%) after 2 h. Potassium carbonate was also used (entry 8) under these conditions, affording 64% of conversion of ketone **4** after 2 h of reaction. In another set of experiments, triethylamine was studied as the base to get access to the desired derivative (entries 9–14). While at room temperature a maximum of 57% of conversion at 24 h was achieved using a 1:1 ratio between **2** and **3** (entry 11), the employment of lower temperatures and a higher amount of 1,3-dichloroacetone afforded very low yields of undesired ketone **6**, although conversions of chlorinated derivative **4** were also low (up to 31%, entries 13 and 14).

To achieve a faster and more efficient synthesis, the reaction was carried out under microwave conditions,[12] studying again different parameters in order to optimize this transformation (Table 2). Thus, when this process was performed in the absence of a base (entries 1–3), even at temperatures of 175 °C the conversion of ketone **4** was extremely low. Therefore, several basic compounds were added into the reaction medium to obtain higher conversions with good selectivities. While the proportion between **2** and **3** was kept 1:3 to minimize the formation of **6**, a substoichiometric amount of the base (0.5 equiv) was selected to compare their efficiency as catalysts, and among them, triethylamine (entry 7), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, entry 11), and potassium carbonate (entry 14) afforded the best results (43–75%) after 10 min at 80 °C, forming disubstituted ketone **6** in very low quantities (<10%). A lower amount of the base (entry 6) or the addition of 1,3-dichloroacetone **3** in portions (entry 13) did not improve the previous results, although leaving the reaction for a longer time (entry 12), slightly enhanced the formation of derivative **4**. Then, the transformations were carried out with these three bases in stoichiometric quantity during 30 min (entries 15–17), and it was clearly observed that K_2CO_3 appeared as the best one affording a high conversion of the desired compound (86%) avoiding the formation of ketone **6**. Gladly, under these conditions and just after 2 min of reaction, the same results were observed (entry 19), and the employment of higher temperatures (entry 20), did not improve the conversion obtained, so conditions shown in entry 19 were selected as the most appropriate to synthesize derivative **4**.

This transformation was achieved at 2 mmol scale obtaining, after 2 min of MW reaction and purification, compound **4** in 78% isolated yield. As the next step, fluorination of this ketone to obtain **5** (Scheme 2), was tried under several conditions. Hence, the use of KF and ZnF_2 in CH_3CN at 120 °C for 24 h;[13] PhCOF, HFIP and DBU in TBME at 50 °C for 24 h;[10] or CsF in CH_3CN under reflux for 24 h in the presence or in the absence of 18-crown-6, did not afford any conversion recovering the starting chlorinated ketone. Due to this, the corresponding chlorohydrin **7** was synthesized by the reduction of **4** using $NaBH_4$ in MeOH at 0 °C in 97% yield, and then the

Table 1
Synthesis of α-chloro ketone **4** by the reaction of nitroimidazole **2** and 1,3-dichloroacetone **3** in the presence of different bases



Entry	Ratio **2**:**3**	Conditions	*t* (h)	**2**[a] (%)	**4**[a] (%)	**6**[a] (%)
1	1:1	CH_2Cl_2, 41 °C, inert atmosphere, Na_2CO_3 (1 equiv)	24	>97	<3	<3
2	1:1	Acetone, rt, Na_2CO_3 (0.5 equiv)	48	28	51	21
3	1:1	Acetone, 56 °C, Na_2CO_3 (0.5 equiv)	24	15	57	28
4	1:1	CH_3CN, rt, Na_2CO_3 (0.5 equiv)	48	40	46	14
5	1:1	CH_3CN, 56 °C, Na_2CO_3 (0.5 equiv)	24	12	58	30
6	1:1	CH_3CN, 82 °C, Na_2CO_3 (0.5 equiv)	2	<3	43	57
7	1:1	CH_3CN, 82 °C, Na_2CO_3 (3 equiv)	2	<3	57	40
8	1:1	CH_3CN, 82 °C, K_2CO_3 (3 equiv)	2	26	64	10
9	1:1	CH_3CN, rt, Et_3N (1 equiv)	1	67	28	5
10	1:1	CH_3CN, rt, Et_3N (1 equiv)	2	57	36	7
11	1:1	CH_3CN, rt, Et_3N (1 equiv)	24	22	57	21
12	1:1	CH_3CN, rt, Et_3N (1 equiv)	48	22	56	22
13	1:2	CH_3CN, 0 °C, Et_3N (1 equiv)	1	80	20	<3
14	1:2	CH_3CN, 0 °C, Et_3N (1 equiv)	2	65	31	4

[a] Measured by ^1H NMR.