

Diastereoselective deacetylative aldol reaction of 3-acetyl-3-fluorooxindoles with aldehydes

Inmaculada Sempere,^{a,b} Cynthia Molina,^{a,b} Eduardo García-Mingüens,^{a,b} M^a de Gracia Retamosa,^{a,b} Carmen Nájera,^{b*} Pedro Merino,^c Miguel Yus,^b and José M. Sansano^{a,b*}

^a Departamento de Química Orgánica and Institute of Organic Synthesis, Universidad de Alicante, Apdo. 99, Ctra. Alicante-San Vicente s/n, 03690-Alicante, Spain

^b Centro de Innovación en Química Avanzada (ORFEO-CINQA), Universidad de Alicante, Apdo. 99, Ctra. Alicante-San Vicente s/n, 03690-Alicante, Spain

^c Departamento de Química Orgánica, Instituto de Biocomputación y Física de Sistemas Complejos (BIFI), Facultad de Ciencias, Universidad de Zaragoza, Campus San Francisco, E-50009 Zaragoza, Spain
Email: cnajera@ua.es; jmsansano@ua.es

Dedicated to Prof. Saverio Florio

Received mm-dd-yyyy

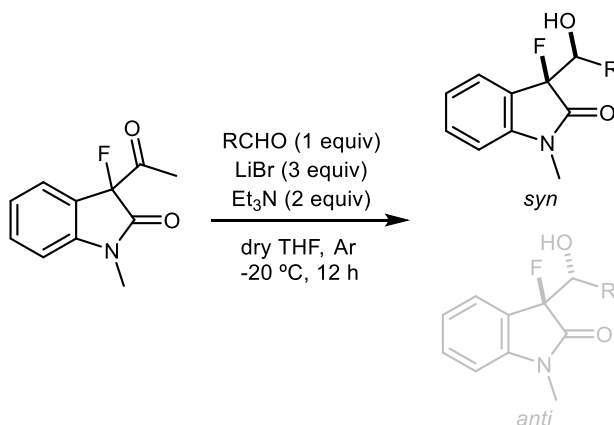
Accepted Manuscript mm-dd-yyyy

Published on line mm-dd-yyyy

Dates to be inserted by editorial office

Abstract

The deacetylative aldol reaction of *N*-methyl-3-acetyl-3-fluoro-2-oxindole is optimized with benzaldehyde and the most appropriate conditions are used for the survey of the scope of this transformation with different aldehydes. The relative configuration of the resulting compounds is also confirmed. The reaction is diastereoselective and affords the *syn*-stereoisomer in good yields. DFT calculations are used for the explanation of this diastereoselectivity through a traditional chair-like transition state.



Keywords: Fluorine, oxindole, deacetylative, aldol, Lewis acid, *syn*-diastereoselectivity, DFT

Introduction

Oxindoles are privileged structures in Nature due to their massive presence in biosynthetic processes.¹ For example, gelsecrotonidine,² welwitindolinones,³ horsfilin,⁴ convolutamidine A⁵ and paratunamides⁶ (Figure 1) possess potent biological activities, which inspired the pharmaceutical industry to synthesize oxindole derivatives with surprising therapeutic effects. In this sense, the incorporation of fluorine to the skeleton is a common strategy.

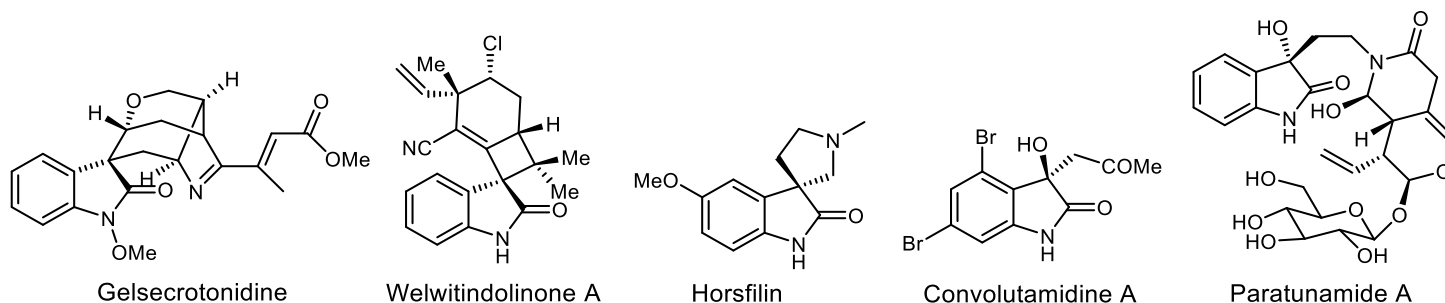


Figure 1. Representative examples of natural products incorporating the oxindole unit.

It is well known that fluorinated compounds exhibit great advantages compared to their non-fluorinated derivatives.^{7,8,9} The substitution of a hydrogen atom, or a hydroxyl group, by a fluorine atom increases metabolic stability and changes in its electronic, electrostatic, lipophilic, and steric properties.^{10,11,12} In the attempt to unify fluorinated-oxindole units the compound called BMS-204352 47 (MaxiPost®) (Figure 2) is commercialized as a neuroprotective drug facilitating the opening of calcium-sensitive maxi-K channels avoiding the ischemic stroke.¹³

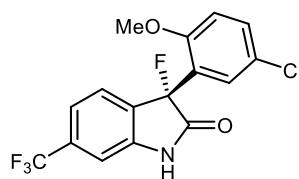
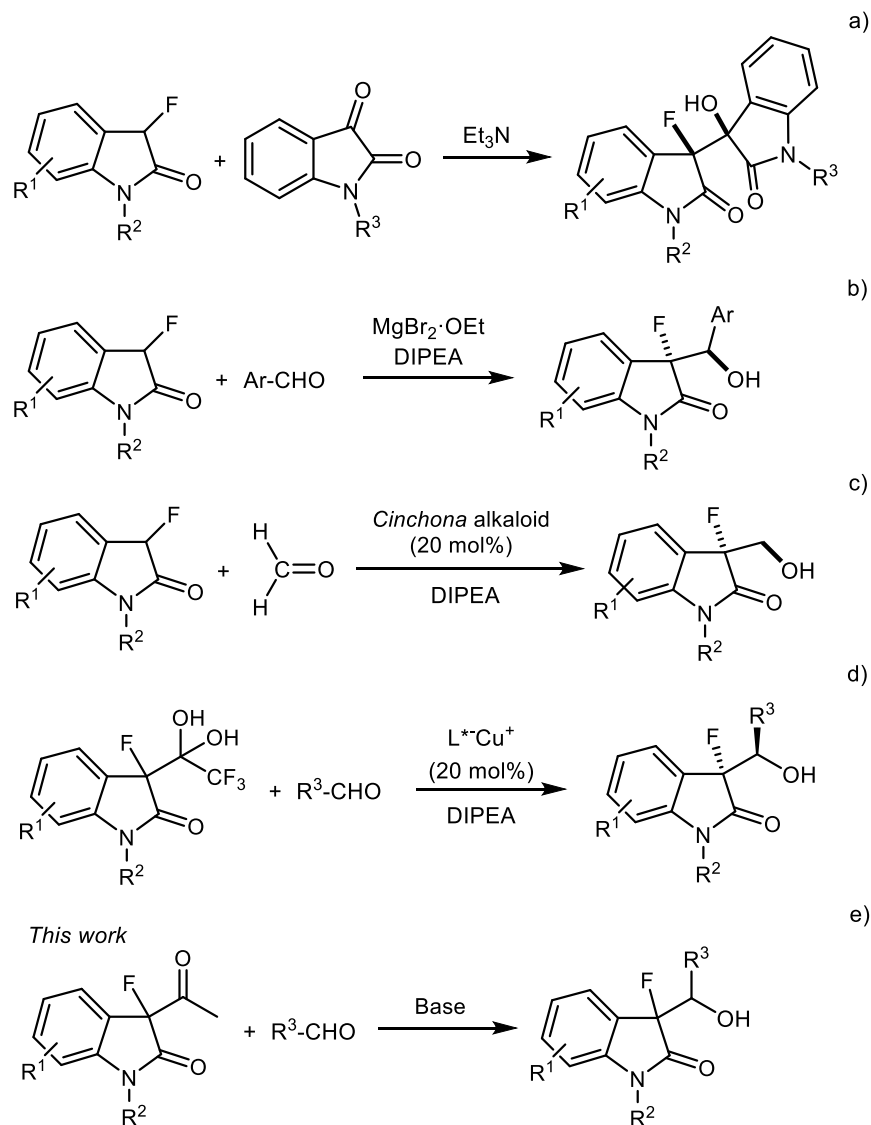


Figure 2. Structure of BMS-204352 (MaxiPost®) or Flindokalner.

In general, 3-substituted 3-fluorooxindoles¹⁴ are prepared by deprotonation of oxindole followed by fluorination with *N*-fluorobenzenesulfonimide (NFSI)^{15,16,17,18} and by fluorination of 3-substituted 3-hydroxyoxindoles with diethylaminosulfur trifluoride (DAST).¹⁹ 3-Fluorooxindoles derivatives have been used, as monofluorinated oxindoleenolates as nucleophiles, in Michael-type additions,^{20,21,22,23} in the Tsuji-Trost reactions,²⁴ and (*via* detrifluoroacetylative alkylations) in Mannich reaction with chiral *N*-*tert*-butanesulfinyl imines^{25,26,27} and in Morita-Baylis-Hillman transformations.²⁸ Focusing our attention in the aldol reaction, involving these types of fluorinated enolates, 3-fluoro-3'-hydroxy-3,3'-bisoxindoles were obtained in high yields by reaction with isatins under mild basic conditions (up to 99 :1 *dr*, Scheme 1a);²⁹ α -fluoro- β -hydroxyoxindoles were diastereoselectively generated by reaction with aromatic aldehydes using MgBr·OEt₂ as Lewis acid (up to 99:1 *anti/syn*, Scheme 1b);³⁰ 3-fluoro-3-

hydroxymethyloxindoles were enantioselectively isolated using a *Cinchona* alkaloid-catalyzed hydroxymethylation with paraformaldehyde (up to 87 :13 *er*, Scheme 1c);³¹ and α -fluoro- β -aryl/hetaryl/alkyl- β -hydroxy-indolin-2-ones through a detrifluoroacetylative addition to aldehydes mediated by a copper(I)-chiral methylenebisoxazolidine (up to 83:17 *dr* and up to 93% *ee*, Scheme 1d).³²



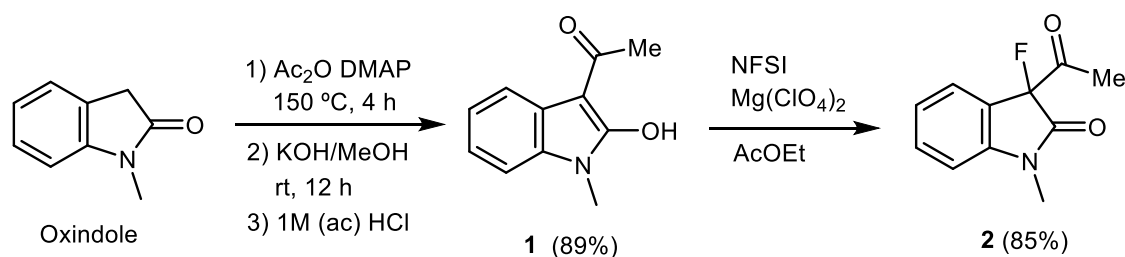
Scheme 1. Aldol reactions involving 3-fluorooxindoles.

In the context of the last example dealing with deacylative alkylations (DaA)³³ of carbon nucleophiles the generation of quaternary stereocenters is one of the main features. First, the acetyl or trifluoroacetyl group can be easily introduced and then, the corresponding carbon nucleophile is generated by a retro-Claisen condensation promoted by a base.^{33,34} Our studies in deacetylative nucleophilic addition onto alkyl halides and electrophilic olefins,^{35,36} and onto π -allyl-palladium systems from allylic alcohols,¹⁴ yielded 3,3'-bioxindoles.³⁷ In addition, the 3-acetyl-3-fluorooxindole was generated and applied to the synthesis of 3-substituted 3-fluorooxindoles by base-promoted alkylation or Michael-type additions and Palladium-catalyzed

DaA,³⁴ but the aldol reaction was not explored yet. So, in this work (Scheme 1e), the optimization and full analysis of the scope of the reaction between 3-acetyl-3-fluorooxindoles and aldehydes as well as some mechanistic details are surveyed.

Results and Discussion

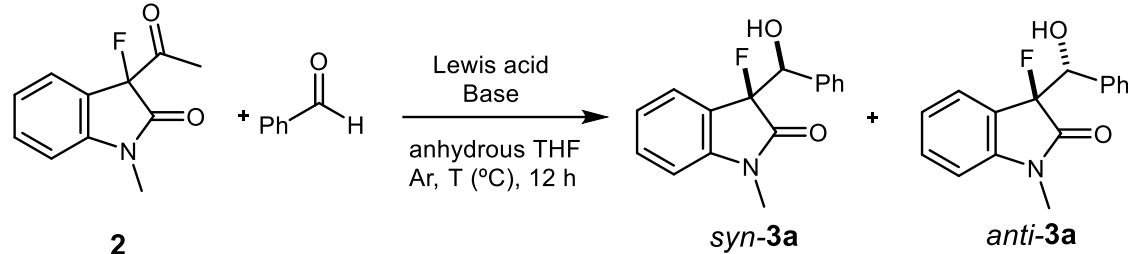
The preparation of the *N*-methyl-3-acetyl-3-fluorooxindole (**2**) was carried out following the procedure detailed in the literature,³⁴ starting from acylation of the commercially available *N*-methyloxindole by means of a Claisen condensation and subsequent isomerization of the carbon-carbon bond in basic media. The resulting compound **1**, isolated in 89% yield, was next fluorinated at the 3-position using NFSI as electrophilic fluorinating agent and $\text{Mg}(\text{ClO}_4)_2$ as Lewis acid in ethyl acetate at room temperature. Despite of the formation of a small amount of the deacetylated fluorinated compound (*N*-methyl-3-fluorooxindol, 8%), the compound **2** was generated in 85% yield.



Scheme 2. Synthesis of the starting fluorooxindole **2**.

Once the substrate **2** was synthesized, the deacetylative alkylation reaction was optimized by using benzaldehyde as reagent in the bench reaction (Table 1). First, the effect of the base was studied. Benzyltrimethylammonium hydroxide (Triton B) and lithium ethoxide were tested at 0 °C giving total conversions but affording complex mixtures in the reaction crude (observed by ¹H NMR) with null diastereoselectivity (Table 1, entries 1 and 2). Cleaner reaction crude with low diastereoselectivity was achieved when the reaction was run in the presence of triethylamine (Table 1, entry 3). Any diastereoselectivity was detected in the reactions mediated by Triton-B at -20 °C with or without LiBr (3 equiv) as additive (Table 1, entries 3 and 5). This additive^{25,26,27} was also employed in the reaction with Et₃N at different temperatures (Table 1, entries 6-11) obtaining the best operational conditions, diastereoselectivity and conversion at -20 °C (Table 1, entry 8). The highest diastereoselectivity determined at -78 °C took place at lower conversions even after 2 days stirring at this temperature (Table 1, entries 10 and 11). Another two additives as $\text{Mg}(\text{ClO}_4)_2$ and LiCl were tested furnishing lower diastereoselectivities and conversions (Table 1, entries 12 and 13). Decreasing the amount of LiBr was not beneficial for the conversion obtaining the deacetylated product (*N*-methyl-3-fluorooxindol) in notable quantities (from crude ¹H NMR) (Table 1, entries 14 and 15). Finally, the employment of anhydrous toluene or dichloromethane as solvents did not improve the result obtained in the reaction run in dry THF (Table 1, entries 16 and 17).

The diastereomeric ratio of **3a** (and for the other family of molecules **3**) was calculated measuring in the crude ¹H NMR spectra the integrals corresponding to the benzylic hydrogen and compared with the analogous already published data. The reported coupling constants for compound **3a** ($J_{\text{F-H}}$) were shown to be 8 and 13.5 Hz for the *syn*-**3a** and *anti*-**3a** diastereoisomers, respectively.³²

Table 1. Optimization of the deacetylative aldol reaction between fluorinated oxindole **2** and benzaldehyde.


Entry	Base	Lewis acid (equiv)	T (°C)	3a , <i>syn:anti</i>	Conv. 3a (%) ^a
1	Triton-B	----	0	50:50	100 ^b
2	LiOEt	----	0	50:50	100 ^b
3	Et ₃ N	----	0	55:45	100
4	Triton-B	----	-20	50:50	100
5	Triton-B	LiBr (3)	-20	50:50	100
6	Et ₃ N	LiBr (3)	0	68:32	100
7	Et ₃ N	LiBr (3)	25	58:42	100
8	Et ₃ N	LiBr (3)	-20	71:29	100
9	Et ₃ N	LiBr (3)	-50	68:32	100
10	Et ₃ N	LiBr (3)	-78	80:20	57
11	Et ₃ N	LiBr (3)	-78	80:20	71 ^c
12	Et ₃ N	Mg(ClO ₄) ₂ (3)	-20	50:50	10
13	Et ₃ N	LiCl (3)	-20	47:53	97
14	Et ₃ N	LiBr (0.5)	-20	70:30	58 ^d
15	Et ₃ N	LiBr (1.5)	-20	62:38	60 ^d
16	Et ₃ N	LiBr (3)	-20	50:50	45 ^e
17	Et ₃ N	LiBr (3)	-20	62:38	68 ^e

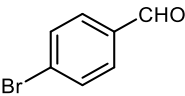
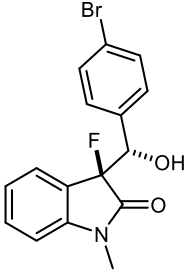
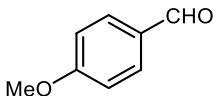
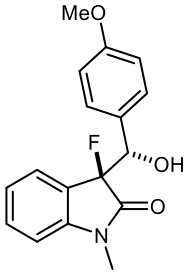
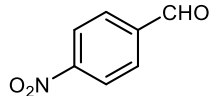
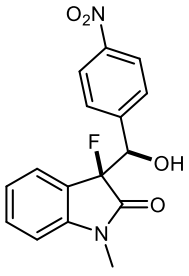
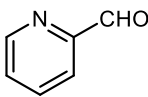
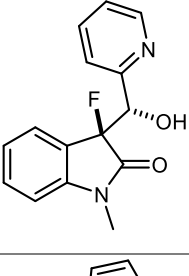
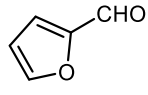
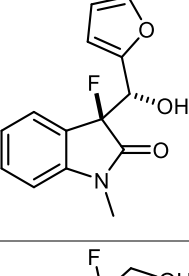

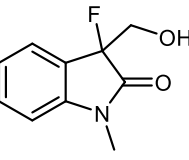
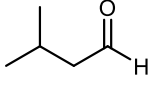
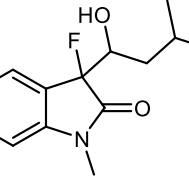
^a Total conversion determined by ¹H NMR of the crude reaction product. In all these examples, deoxygenated solvents (freezing pump procedure) were employed. ^b Very complex reaction crudes were observed by ¹H NMR. ^c The reaction was stirred at -78 °C for 2 days. ^d Starting material **2** and the corresponding deacylated compound were identified in the crude ¹H NMR. ^e Reaction performed in toluene. ^f Reaction performed in dichloromethane.

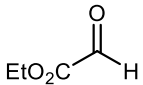
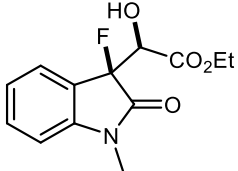
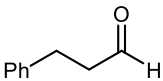
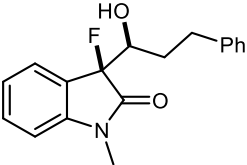
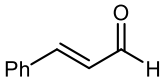
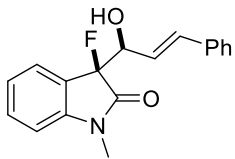
The reaction with assorted aldehydes was studied employing LiBr (3 equiv) in anhydrous THF, at -20 °C for 12 h (Table 2, entries 1-7). *Ortho*-substituents diminished the chemical yields, whilst *meta*- or *para*-substituents afforded similar yields and in the range of the non-substituted aromatic aldehydes. Electron-donating and electron-withdrawing groups in the aromatic ring of the aldehyde are appropriate substrates for this reaction. In the particular example of 4-nitrobenzaldehyde, a reverse diastereoselectivity was observed obtaining the *anti*-**3g** aldol in a 70:30 ratio. This effect was also detected, but in not so large extension, in the published enantioselective addition (Table 2, entry 7).³² Heteroaromatic aldehydes were also good precursors affording good yields and notable *syn*-diastereoselectivity (Table 2, entries 8 and 9). Formaldehyde furnished a very high yield (90%) of the corresponding 3-hydroxymethyloxindole **3j** (Table 2, entry 10). Ethyl glyoxylate

and dihydrocinnamaldehyde afforded the highest *syn*-diastereoselectivities of this series of molecules in good yields (Table 2, entries 12 and 13). However, isovaleraldehyde gave a very low conversion of an equimolar amount of diastereoisomers, which could not be isolated after column chromatography (flash silica-gel) (Table 2, entry 11). Finally, the discrimination between aldol reaction vs Michael-type addition was assessed in the presence of cinnamaldehyde (Table 2, entry 14). The aldol reaction proved to be faster than the Michael-type addition, giving rise to aldol **3n** in 85% yield and any traces of 1,4-addition were detected.

Table 2. Deacetylative aldol reaction of fluorooxindole **2**.

Entry	Aldehyde	3	Structure	Yield (%) ^a	<i>dr</i> ^b
1		3a		60	71:29
2		3b		43	60:40
3		3c		62	79:21
4		3d		69	84:16

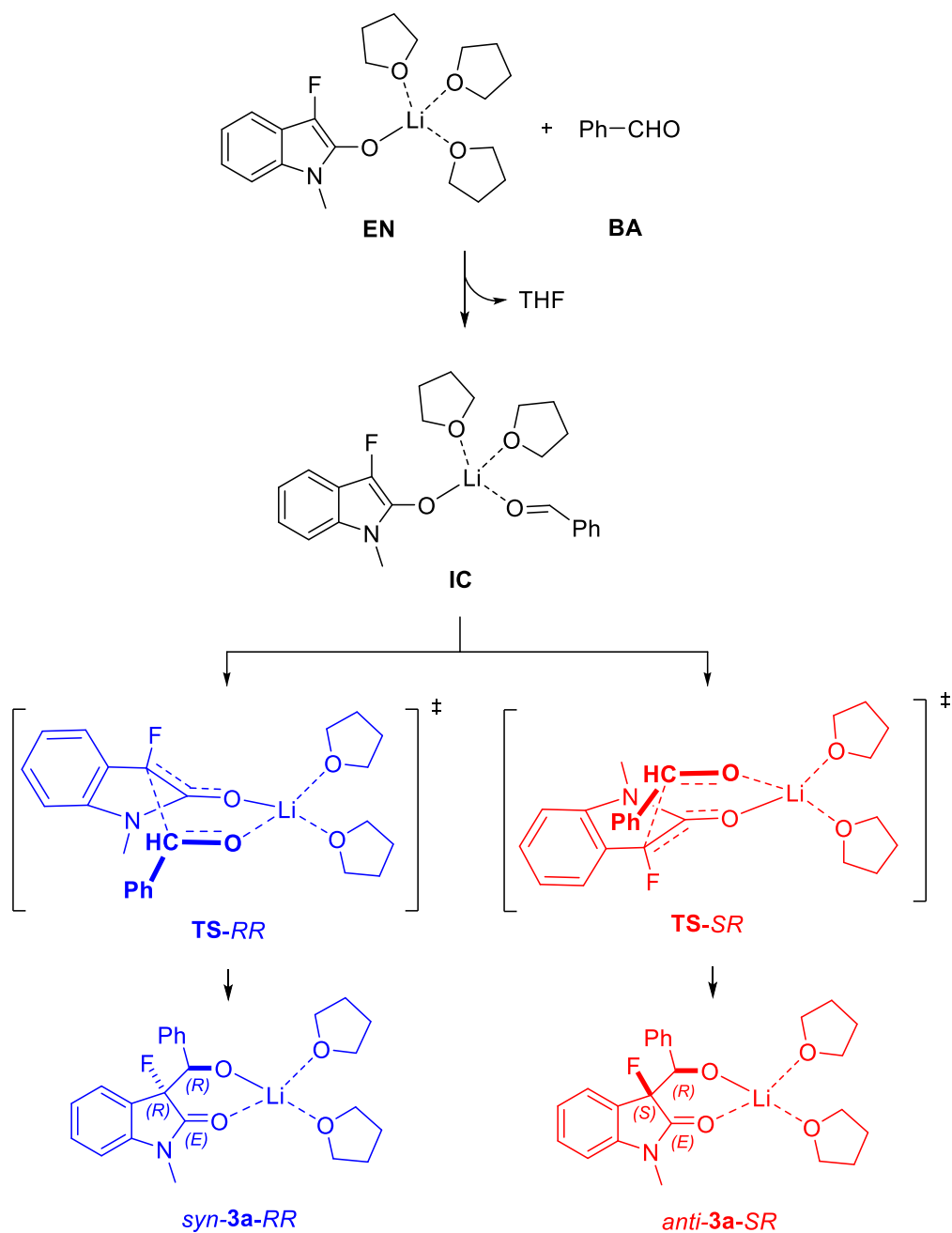
5		3e		59	68:32
6		3f		55	67:33
7		3g		90	30:70
8		3h		80	64:36
9		3i		61	72:28
10		3j		90	---
11		3k		42	50 :50 ^c

12		3l		80	80:20
13		3m		74	90:10
14		3n		83	88:12

^a Yield of the major diastereoisomer purified by flash chromatography. In all these examples, deoxygenated solvents (freezing pump procedure) were employed. ^b Ratio determined by ¹H NMR of the crude product. ^c Conversion estimated by ¹H NMR.

In order to explain the generation of the major *syn*-diastereoselectivity, the transition states energies were calculated using DFT calculations. The lithium enolate (**EN**) is coordinated to several THF molecules, stabilizing it, and then, it coordinates with the benzaldehyde (**BA**) to form the intermediate complex (**IC**). **IC** immediately rearranges to give rise to the two possible diastereomeric transition states **TS-RR** and **TS-SR** (Scheme 3). The computational analysis revealed an energy gap between them of 2.4 kcal·mol⁻¹, transition state TS-RR being the most stable, which justifies the generation of the major product *syn*-**3a** (Figure 3). It was also found that the *syn*-diastereoisomer is more stable than the *anti*-diastereoisomer around 3.3 kcal·mol⁻¹ (Figure 3).

In the **TS-RR** transition state, it is observed that the aromatic ring of the enolate (more deficient in electronic density than in the starting reagent **2**) presents a key π -type electrostatic interaction with the arene group of the aldehyde with a certain charge density, such as occurred in the example of benzaldehyde. This effect would be favored by the presence of substituents that promote transfer of charge to the aromatic ring of the corresponding aldehyde (Me, OMe or even Br). However, the presence of a substituent that removes a high charge density (as occurred with the nitro group) possibly contributes to a greater repulsion between the aromatic resulting, in this case, that the **TS-RS** transition state is much more stable allowing the aldol reaction faster.



Scheme 3. Intermediate species and transition states defined in the stereochemical course of the aldol reaction to generate the reaction products *syn*-3a-RR and *anti*-3a-SR (racemates).

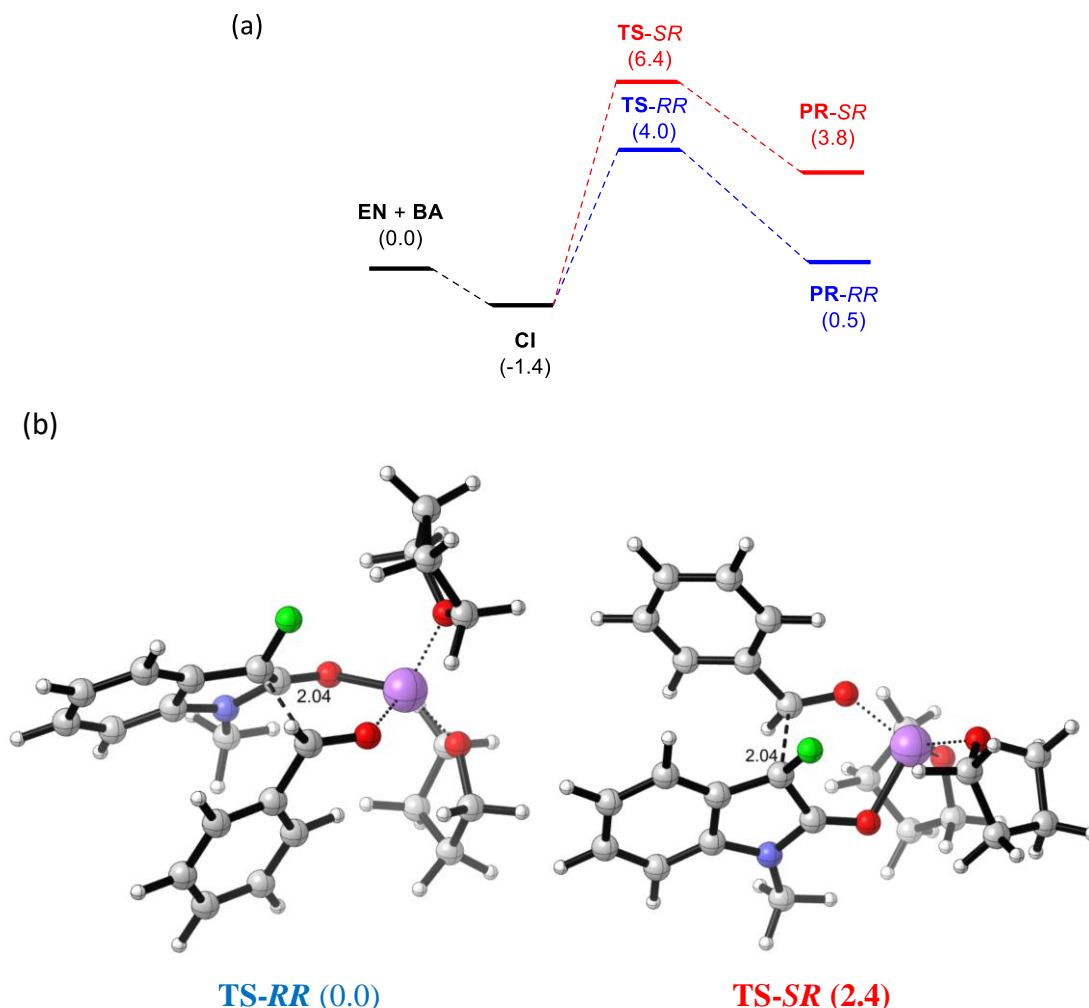


Figure 3. (a) Energy profile of all the species involved in the studied process. (b) **TS-RR** and **TS-SR** transition states. The relative energies ($\text{kcal}\cdot\text{mol}^{-1}$) appear in parentheses and the distances are measured in Å. The analysis calculation level is b3lyp-3dbj/def2tzvp/PCM=THF//b3lyp-3dbj/def2svp/PCM=THF.

Conclusions

In this study it was demonstrated the efficiency of the non-asymmetric deacetylated aldol reaction of the *N*-methyl-3-acetyl-3-fluoro-2-oxindole under very mild conditions generating a quaternary center after this carbon-carbon bond formation. Despite a non-asymmetric process, the titled reaction can be compared with the enantioselective version from the corresponding detrifluoroacetylated process published by Soloshonok *et al.* In general, chemical yields and diastereomeric ratios are in the same range in both studies. Also, the temperature ($-20\text{ }^{\circ}\text{C}$) is a common feature, but, from the atom economy point of view, the methodology described here is more advantageous. Among them, it has been found that an intense π -type electrostatic interaction is the driving force that allowed the *syn*-diastereoselectivity when electron-rich aromatic aldehydes participated in the reaction. However, electron-withdrawing groups bonded to the aromatic rings did not favor this interaction increasing the *anti*-diastereoselectivity. At this moment, several representative examples of the reported molecules are being tested in parallel biological activity programs.

Experimental Section

General. All commercially available reagents (Acros, Aldrich, Fluka, Fluorochem and Merck) were used without prior purification. In all these examples, deoxygenated solvents (freezing pump procedure) were employed. Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. IR spectra were collected with a FT-IR 4100LE (JASCO) (PIKE MIRacle ATR). The nuclear magnetic resonance experiments of proton and fluorine ^1H NMR and ^{19}F NMR (282 MHz, using trifluoroacetic acid as internal reference) and carbon ^{13}C NMR (75 MHz) were carried out in the Nuclear Magnetic Resonance units of the Research Technical Services of the University of Alicante with the Bruker Avance AC-300 spectrophotometer and using deuterated chloroform and tetramethylsilane (TMS) as internal standard, unless otherwise indicated. Chemical shifts (δ) are given in ppm and coupling constants (J) in Hz. The following abbreviations are used to describe the multiplicity of signals: s (singlet), d (doublet), t (triplet), m (multiplet), bs (broad singlet). The *rd* value of the products is determined by the ^1H NMR spectrum. The low-resolution mass spectrometry analyzes by electron impact (IE) were carried out in the Mass Spectrometry units of the same service with a Shimadzu QP-5000 by DIP injection (Direct Introduction Probe), and high-resolution mass spectra were obtained with a Finnigan MAT 95S. Ions arising from the breaks are given as m/z with relative percentage intensities in parentheses. For the thin-layer chromatography (TLC) technique, prefabricated Schleicher & Schuell F1400/LS 254 silica chromatoplates were used and the results were visualized under UV light ($\lambda = 254$ nm). Flash chromatography was performed with silica gel 60, 0.04-0.06mm. For general computational details, please, see supporting information.

General procedure for the synthesis of 3-acetyl-2-hydroxy-1-methyl-1H-indole (1). A round bottom flask was charged with 1 equiv of 1-methylindolin-2-one (4.71 g, 32 mmol), DMAP (117.3 mg, 0.96 mmol, 0.03 equiv) and acetic anhydride 1 M, (32 mL) and the mixture was heated at reflux (140 °C) for 5 h and then evaporated under reduced pressure. The residue was dissolved in MeOH (80 mL), then a solution of KOH 90% (18 g, 289 mmol, 9 equiv) in MeOH (120 mL) at 0 °C was added. The solution was stirred at room temperature for 22 h and then cooled in an ice-bath at 0 °C. A solution of 12 M aqueous HCl (25 mL) was added until pH 2. The organic solvent was evaporated, and the residue was extracted with EtOAc (3 × 50 mL), washed with H₂O (50 mL), dried over MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography (*n*-hexane:EtOAc 9:1) to obtain pure compound **1**.

General procedure for the synthesis of 3-acetyl-3-fluoro-1-methylindolin-2-one (2). In a round-bottom flask that contains a solution of compound **1** (8 mmol) and Mg(ClO₄)₂ (0.54 g, 2.4 mmol 0.3 equiv) in ethyl acetate (160 mL) was stirred for 5 min. Then, NFSI (2.77 g, 8.8 mmol, 1.1 equiv) was added. The reaction was stirred overnight at room temperature and an extractive work-up was performed with (80 mL x 3) of EtOAc in 80 mL of H₂O, drying the organic phases with MgSO₄, filtering and concentrating. The resulting crude product was purified by flash chromatography (toluene:ethyl acetate, 9.5:0.5) to obtain pure compounds **2**.³⁴

General procedure for the synthesis of compounds 3. In a Schlenk tube, previously dried and under argon, was charged with 3-acetyl-3-fluoro-1-methylindolin-2-one (**2**) (62.16 mg, 0.3 mmol, 1 equiv), the corresponding aldehyde (0.3 mmol, 1 equiv), LiBr (78.16 mg, 0.9 mmol, 3 equiv) and it was dissolved in dried and deoxygenated THF (3 mL). The reaction mixture was cooled at -20 °C and triethylamine (84 μL , 0.6 mmol) was slowly added and stirred overnight. Then, the solvent was evaporated under reduced pressure and the crude mixture was extracted 3 times with EtOAc (15 mL) and water (15 mL). The organic layers were mixed,

dried over MgSO₄, and concentrated under vacuum. The final products were purified by column chromatography (flash silica-gel) using EtOAc:toluene (2:8) as eluent.

(RS)-3-Fluoro-3-[(RS)-hydroxy(phenyl)methyl]-1-methylindolin-2-one (3a).³² White solid, 49 mg, 60% yield, from crude 71:29 *dr*; mp 114-115 °C (from EtOAc:toluene) (lit.³² 115-116 °C); ¹H NMR (400 MHz, CDCl₃) δ: 7.36–7.28 (m, 6H), 6.94 (t, *J* 7.6 Hz, 1H), 6.74 (d, *J* 7.8 Hz, 1H), 6.64 (d, *J* 7.3 Hz, 1H), 5.45 (dd, *J* 8.1, 4.4 Hz, 1H), 3.12 (s, 3H), 3.09 (bs, 1H) ppm; ¹⁹F NMR (282 MHz, CDCl₃) δ: -162.53 (s, 1F) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 172.8 (d, *J* 20.5 Hz), 145.1 (d, *J* 5.5 Hz), 137.0, 131.6 (d, *J* 2.9 Hz), 128.6, 128.0, 127.4 (d, *J* 1.8 Hz), 126.2, 123.1, 122.8 (d, *J* 2.8 Hz), 108.7, 93.2 (d, *J* 192.9 Hz), 74.5 (d, *J* 31.1 Hz), 26.29 ppm; FT-IR (ATR) ν_{\max} : 3352, 3062, 1691, 1616, 1469, 1378, 1195, 1057, 1014, 744, 698 cm⁻¹. GC/MS (EI) *m/z* (%): 77 (100), 164 (90), 194 (84), 271 (M⁺, 9).

(RS)-3-Fluoro-3-[(RS)-hydroxy(*o*-tolyl)methyl]-1-methylindolin-2-one (3b).³² White solid, 37 mg, 43% yield, from crude 60:40 *dr*; mp 148-150 °C (from EtOAc:toluene) (lit.³² 145-147 °C); ¹H NMR (400 MHz, CDCl₃) δ: 7.35 (t, *J* 7.8 Hz, 1H), 7.31–7.20 (m, 2H), 7.18 (t, *J* 8.0 Hz, 2H), 6.79 (d, *J* 7.6 Hz, 1H), 6.80 (d, *J* 7.8 Hz, 1H), 6.72 (d, *J* 7.5 Hz, 1H), 5.75 (t, *J* 5.4 Hz, 1H), 3.19 (s, 3H), 2.74 (d, *J* 5.2 Hz, 1H), 2.43 (s, 3H) ppm. ¹⁹F NMR (282 MHz, CDCl₃) δ: -163.20 (s, 1F) ppm; ¹³C NMR (75 MHz, CDCl₃) δ: 173.3 (d, *J* 20.4 Hz), 145.3 (d, *J* 5.6 Hz), 137.2, 135.6, 131.5 (d, *J* 3.0 Hz), 130.7, 128.5, 127.9, 127.1, 125.3, 122.8 (d, *J* 18.4 Hz), 122.5 (d, *J* 2.8 Hz), 108.6, 94.3 (d, *J* 191.9 Hz), 70.6 (d, *J* 33.5 Hz), 26.4, 19.9 (d, *J* 5.9 Hz) ppm; FT-IR (ATR) ν_{\max} : 3375, 2927, 1708, 1616, 1466, 1423, 1373, 1215, 1099, 1049, 1011, 748, 694 cm⁻¹; GC/MS (EI) *m/z* (%): 65 (21), 91 (100), 119 (84), 120 (90), 207 (23), 285 (M⁺, 6).

(RS)-3-Fluoro-3-[(RS)-hydroxy(*m*-tolyl)methyl]-1-methylindolin-2-one (3c).³² White solid, 53 mg, 62% yield, from crude 79:21 *dr*; mp 250-252 °C (from EtOAc:toluene) (lit.³² 249-250 °C); ¹H NMR (300 MHz, CDCl₃) δ: 7.32 (t, *J* 7.8 Hz, 1H), 7.23 - 7.14 (m, 1H), 7.14–7.04 (m, 3H), 6.93 (t, *J* 7.6 Hz, 1H), 6.74 (d, *J* 7.9 Hz, 1H), 6.63 (dd, *J* 7.4, 1.7 Hz, 1H), 5.40 (d, *J* 8.1, 1H), 3.12 (s, 3H), 2.30 (s, 3H); ¹⁹F NMR (376 MHz, CDCl₃) δ: -162.69 (s, 1F); ¹³C NMR (75 MHz, CDCl₃) δ: 172.9 (d, *J* 20.7 Hz), 145.1 (d, *J* 5.4 Hz), 137.6, 136.9, 131.5 (d, *J* 3.0 Hz), 129.2, 128.1 (d, *J* 2.0 Hz), 127.8, 126.4, 124.3 (d, *J* 1.89 Hz), 123.0 (d, *J* 18.2 Hz), 122.7 (d, *J* 2.7 Hz), 108.7, 93.2 (d, *J* 192.72 Hz), 74.5 (d, *J* 31.2 Hz), 26.3, 21.5; FT-IR (ATR) ν_{\max} : 3294, 1700, 1616, 1469, 1381, 1257, 1157, 1099, 1065, 1011, 748 cm⁻¹; GC/MS (EI) *m/z* (%): 65 (2), 91 (100), 119 (97), 120 (97), 207 (3), 285 (M⁺, 2).

(RS)-3-Fluoro-3-[(RS)-hydroxy(*p*-tolyl)methyl]-1-methylindolin-2-one (3d).³² White solid, 59 mg, 69% yield, from crude 84:16 *dr*; mp 130-132 °C (from EtOAc:toluene) (lit.³² 132-133 °C); ¹H NMR (400 MHz, CDCl₃) δ: 7.30 (tt, *J* 7.8, 1.5 Hz, 1H), 7.17 (d, *J* 7.3 Hz, 2H), 7.09 (d, *J* 6.9 Hz, 2H), 6.91 (t, *J* 7.6 Hz, 1H), 6.73 (d, *J* 7.9 Hz, 1H), 6.60 (dt, *J* 7.5, 1.5 Hz, 1H), 5.37 (dd, *J* 8.1, 5.3 Hz, 1H), 3.42 (d, *J* 5.7 Hz, 1H), 3.10 (s, 3H), 2.32 (s, 3H) ppm; ¹⁹F NMR (282 MHz, CDCl₃) δ: -162.75 (s, 1F); ¹³C NMR (101 MHz, CDCl₃) δ: 172.9 (d, *J* 20.6 Hz), 145.1 (d, *J* 5.5 Hz), 138.1, 134.1, 131.4 (d, *J* 2.9 Hz), 128.6, 127.3 (d, *J* 2.0 Hz), 126.3, 123.0 (d, *J* 18.3 Hz), 122.6 (d, *J* 2.7 Hz), 108.6, 93.1 (d, *J* 191.9 Hz), 74.0 (d, *J* 31.3 Hz), 26.2, 21.3 ppm. FT-IR (ATR) ν_{\max} : 3295, 1700, 1615, 1466, 1381, 1255, 1155, 1101, 1065, 1011, 749 cm⁻¹; GC/MS (EI) *m/z* (%): 65 (12), 91 (100), 119 (90), 120 (99), 207 (33), 285 (M⁺, 12).

(RS)-3-[(RS)-(4-Bromophenyl)(hydroxy)methyl]-3-fluoro-1-methylindolin-2-one (3e).³² White solid, 62 mg, 59% yield, from crude 68:32 *dr*; mp 144-145 °C (from EtOAc:toluene) (lit.³² 145-146 °C); ¹H NMR (300 MHz, CDCl₃) δ: 7.44 (d, *J* 8.5 Hz, 2H), 7.35 (tt, *J* 7.8, 1.5 Hz, 1H), 7.19 (d, *J* 8.2 Hz, 2H), 6.97 (t, *J* 7.6 Hz, 1H), 6.77 (d, *J*

7.9 Hz, 1H), 6.64 (dt, *J* 7.5, 1.5 Hz, 1H), 5.41 (d, *J* 7.9 Hz, 1H) ppm; ^{19}F NMR (282 MHz, CDCl_3) δ : -162.53 (s, 1F) ppm; ^{13}C NMR (101 MHz, CDCl_3) δ : 172.6 (d, *J* 20.7 Hz), 145.0 (d, *J* 5.7 Hz), 136.0, 131.6 (d, *J* 2.9 Hz), 131.0, 129.0 (d, *J* 1.6 Hz), 126.1, 122.9 (d, *J* 2.8 Hz), 122.6, 122.4, 108.8, 92.8 (d, *J* 193.1 Hz), 73.7 (d, *J* 31.4 Hz), 26.3 ppm; FT-IR (ATR) ν_{max} : 3367, 3047, 2939, 1691, 1616, 1469, 1381, 1103, 1065, 1011, 818, 756, 698 cm^{-1} . GC/MS (EI) *m/z* (%): 50 (28), 75 (25), 154 (42), 183 (100), 349 (M^+ , 0.6) 351 (M^+ , 0.6).

(RS)-3-Fluoro-3-[(RS)-hydroxy(4-methoxyphenyl)methyl]-1-methylindolin-2-one (3f).³² White solid, 50 mg, 55% yield, from crude 67:33 *dr*; m.p: 129-130 °C (from EtOAc:toluene) (lit.³² 105-106 °C); ^1H NMR (400 MHz, CDCl_3) δ : 7.33 (tt, *J* 7.8, 1.5 Hz, 1H), 7.21 (d, *J* 8.5 Hz, 2H), 6.95 (tt, *J* 7.6, 0.9 Hz, 1H), 6.88–6.80 (m, 2H), 6.74 (d, *J* 7.9 Hz, 1H), 6.70 (dt, *J* 7.4, 1.5 Hz, 1H), 5.39 (d, *J* 8.2 Hz, 1H), 3.80 (s, 3H), 3.13 (s, 3H), 3.04 (bs, 1H) ppm; ^{19}F NMR (282 MHz, CDCl_3) δ : -162.58 (s, 1F) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ : 172.8 (d, *J* 21.03 Hz), 159.8, 145.1 (d, *J* 5.5 Hz), 131.5 (d, *J* 2.9 Hz), 129.0 (d, *J* 1.0 Hz), 128.6 (d, *J* 1.8 Hz), 126.3, 123.1 (d, *J* 18.7 Hz), 122.8 (d, *J* 2.7 Hz), 113.4, 108.7, 93.2 (d, *J* 192.3 Hz), 74.3 (d, *J* 31.3 Hz), 55.4, 26.3 ppm; FT-IR (ATR) ν_{max} : 3375, 1691, 1612, 1508, 1469, 1419, 1377, 1308, 1254, 1176, 1103, 1037, 833, 744, 683 cm^{-1} . GC/MS (EI) *m/z* (%): 149 (25), 164 (42), 194 (100), 300 (M^+-1 , 0.6) 301 (M^+ , 5).

(RS)-3-Fluoro-3-[(RS)-hydroxy(4-nitrophenyl)methyl]-1-methylindolin-2-one (3g).³² Pale yellow solid, 85 mg, 90% yield, from crude 30:70 *dr*; mp 110-112 °C (from EtOAc:toluene) (lit.³² 96-97 °C); ^1H NMR (400 MHz, CDCl_3) δ : 8.0 (m, 2H), 7.41 (d, *J* 7.4 Hz, 1H), 7.32 (m, 3H), 7.06 (t, *J* 7.6 Hz, 1H), 6.62 (d, *J* 7.9 Hz, 1H), 5.56 (dd, *J* 12.3, 2.0 Hz, 1H), 3.15 (s, 3H) ppm; ^{19}F NMR (282 MHz, CDCl_3) δ : -166.87 (s, 1F) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ : 121.0 (d, *J* 20.9 Hz), 144.4 (d, *J* 5.1 Hz), 131.7, 125.5, 124.1 (d, *J* 18.5 Hz), 123.6, 109.0, 91.7 (d, *J* 189.7 Hz), 64.5 (d, *J* 30.5 Hz), 26.4 ppm; FT-IR (ATR) ν_{max} : 2935, 1724, 1616, 1473, 1369, 1241, 1103, 1052, 929, 755 cm^{-1} ; GC/MS (EI) *m/z* (%): 43 (14), 164 (6), 165 (100), 237 (23), 316 (M^+ , 0.2).

(RS)-3-Fluoro-3-[(RS)-hydroxy(pyridin-2-yl)methyl]-1-methylindolin-2-one (3h). White solid, 66 mg, 80% yield, from crude 64:36 *dr*; mp 118-121 °C (from EtOAc:toluene); ^1H NMR (400 MHz, CDCl_3) δ : 8.56 (dt, *J* 4.9, 1.4 Hz, 1H, CHAr), 6.84–6.73 (m, 1H, CHAr), 5.90 (dddd, *J* 7.5, 2.0, 1.3, 0.6 Hz, 1H), 5.41 (t, *J* 5.3 Hz, 1H), 4.99 (d, *J* 6.4 Hz, 1H), 3.25 (s, 1H); ^{19}F NMR (282 MHz, CDCl_3) δ : -163.35 ppm; ^{13}C NMR (75 MHz, CDCl_3) δ : 172.3 (d, *J* 19.7 Hz), 154.7, 147.8, 146.0, 137.0, 131.6 (d, *J* 2.8 Hz), 125.7, 124.0, 123.5, 123.4, 122.4, 108.6, 93.0 (d, *J* 193.1 Hz), 71.6 (d, *J* 31.6 Hz), 26.6 ppm; FT-IR (ATR) ν_{max} : 3062, 2965, 2842, 1727, 1608, 1469, 1373, 1245, 1153, 1103, 1064, 1010, 867, 809, 752, 694 cm^{-1} ; GC/MS (EI) *m/z* (%): 78 (11), 108 (100), 165 (36), 272 (M^+ , 0.1); HRMS: [M^+ (-FOH)] = 236.0948; found: 236.0961; EA required for $\text{C}_{15}\text{H}_{13}\text{FN}_2\text{O}_2$: C 66.2, H 4.8, N 10.3%; found: C 66.5, H 4.7, N 10.4%.

(RS)-3-Fluoro-3-[(RS)-fur-2-yl(hydroxy)methyl]-1-methylindolin-2-one (3i). Pale yellow solid, 48 mg, 61% yield, from crude 72:28 *dr*; mp 110-111 °C (from EtOAc:toluene); ^1H NMR (400 MHz, CDCl_3) δ : 7.41–7.32 (m, 2H), 7.08–6.93 (m, 2H), 6.80 (d, *J* 8.0 Hz, 1H), 6.36–6.28 (m, 2H), 5.41 (d, *J* 7.6 Hz, 1H), 3.36 (bs, 1H), 3.18 (s, 3H) ppm; ^{19}F NMR (282 MHz, CDCl_3) δ : -163.27 (s, 1F) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ : 172.2 (d, *J* 20.8 Hz), 150.6 (d, *J* 3.0 Hz), 145.1 (d, *J* 5.3 Hz), 142.7, 131.8 (d, *J* 3.1 Hz), 125.9, 123.3 (d, *J* 2.6 Hz), 122.8 (d, *J* 18.2 Hz), 110.8, 109.1 (d, *J* 1.6 Hz), 92.0 (d, *J* 193.9 Hz), 69.9 (d, *J* 33.2 Hz), 26.4 ppm; FT-IR (ATR) ν_{max} : 3383, 2947, 1709, 1612, 1469, 1380, 1211, 1146, 1065, 1011, 937, 856, 818, 741 cm^{-1} ; GC/MS (EI) *m/z* (%): 97 (13), 136 (6), 150 (5), 165 (100), 261 (M^+ , 0.01); HRMS: [M^+ (-FOH)] = 225.2439; found: 225.2436; EA required for $\text{C}_{14}\text{H}_{12}\text{FNO}_3$: C 64.4, H 4.6, N 5.4%; found: C 64.5, H 4.7, N 5.4%.

3-Fluoro-3-(hydroxymethyl)-1-methylindolin-2-one (3j).³¹ Colourless prisms, 53 mg, 90% yield; mp 100 °C (from EtOAc:toluene) (lit.^{31,32} 100-101 °C); ¹H NMR (400 MHz, CDCl₃) δ: 7.51 (dddd, *J* 7.4, 2.0, 1.3, 0.6 Hz, 1H), 7.45–7.37 (m, 1H), 7.19–7.06 (m, 1H), 6.92–6.81 (m, 1H), 4.19–3.97 (m, 1H), 3.21 (s, 2H) ppm. ¹⁹F NMR (282 MHz, CDCl₃) δ: -166.89 (s, 1F) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 172.0 (d, *J* 20.9 Hz), 144.4 (d, *J* 5.1 Hz), 131.7, 125.5, 124.15 (d, *J* 18.7 Hz), 123.6, 109.0, 91.7 (d, *J* 189.6 Hz), 64.5 (d, *J* 30.6 Hz), 26.4 ppm; FT-IR (ATR) ν_{\max} : 2935, 1724, 1616, 1473, 1369, 1241, 1103, 1052, 929, 755 cm⁻¹. GC/MS (EI) *m/z* (%): 43.1 (14), 164 (6), 165.1 (100), 195 (M⁺, 0.1); HRMS: calcd. M⁺ = 195.0696; found: 195.0704.

Ethyl (RS)-2-[(RS)-3-fluoro-1-methyl-2-oxoindolin-3-yl]-2-hydroxyacetate (3l). White solid, 64 mg, 80% yield, from crude 80:20 *dr*; mp 133-135 °C (from EtOAc:toluene); ¹H NMR (400 MHz, CDCl₃) δ: 7.58–7.37 (m, 1H), 7.25 (s, 1H), 7.10 (dd, *J* 4.7, 3.8 Hz, 1H), 6.86 (d, *J* = 7.9 Hz, 1H), 4.80 (dd, *J* 8.6, 6.3 Hz, 1H), 4.31 (qd, *J* 7.1, 0.7 Hz, 1H), 3.22 (s, 1H), 1.29 (t, *J* 7.1 Hz, 1H). ¹⁹F NMR (282 MHz, CDCl₃) δ: -166.28 (s, 1F) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: ppm; FT-IR (ATR) ν_{\max} : 3424, 2923, 2850, 1731, 1612, 1469, 1369, 1307, 1222, 1087, 1018, 752 cm⁻¹; GC/MS (EI) *m/z* (%): 146 (11), 164 (53), 165 (100), 166 (10), 194 (7), 267 (M⁺, 18); HRMS: calcd. M⁺ = 267.0907, found: 267.0913; EA required for C₁₃H₁₄FNO₄: C 58.4, H 5.3, N 5.2%; found: C 58.5, H 5.6, N 5.4%.

(RS)-3-Fluoro-3-[(RS)-1-hydroxy-3-phenylpropyl]-1-methylindolin-2-one (3m). Colorless oil, 66 mg, 74% yield, from the crude 47:53 *dr*; ¹H NMR (400 MHz, CDCl₃) δ: 7.62 (d, *J* 7.4 Hz, 1H), 7.44–7.30 (m, 2H), 7.33–7.02 (m, 12H), 6.80–6.65 (m, 1H), 4.44–4.24 (m, 1H), 3.16 (s, 4H), 2.93–2.85 (m, 1H), 2.67–2.57 (m, 1H), 1.43–1.34 (m, 1H); ¹⁹F NMR (282 MHz, CDCl₃) δ: (s, 1F) -163.43 ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 171.8 (d, *J* 20.7 Hz), 144.6, 144.6, 141.4, 131.5, 131.5, 128.6, 128.5, 126.8, 126.1, 123.6, 123.4, 108.8, 954.4 (d, *J* 187.5 Hz), 73.23 (d, *J* 25.6 Hz), 31.4, 26.4 ppm; FT-IR (ATR) ν_{\max} : 3058, 2935, 2360, 1727, 1616, 1469, 1373, 1265, 1083, 1022, 1103, 1052, 929, 755 cm⁻¹; GC/MS (EI) *m/z* (%): 91 (28), 117 (7), 164 (9), 165 (100), 166 (18), 299 (M⁺, 12); HRMS: calcd. M⁺ = 299.1322, found: 299.1326. EA required for C₁₈H₁₈FNO₂: C 72.2, H 6.1, N 4.7%; found: C 72.5, H 5.9, N 5.0%.

(R)-3-Fluoro-3-[(R,E)-1-hydroxy-3-phenylallyl]-1-methylindolin-2-one (3n). Colorless oil, 74 mg, 83% yield, from crude 34:66 *dr*; ¹H NMR (400 MHz, CDCl₃) δ: 7.68–7.51 (m, 1H), 7.49–7.34 (m, 1H), 7.27–7.16 (m, 2H), 7.14 (dd, *J* 4.7, 3.8 Hz, 1H), 6.83 (d, *J* 7.9 Hz, 1H), 6.71 (d, *J* 15.9 Hz, 1H), 6.09 (ddd, *J* 10.2, 8.2, 0.9 Hz, 1H), 5.74 (ddd, *J* 15.9, 8.3, 0.7 Hz, 1H), 3.13 (s, 1H); ¹⁹F NMR (282 MHz, CDCl₃) δ: -164.34 (s, 1F) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 169.5, 144.8, 137.9, 135.7, 131.9, 128.7, 127.0, 126.6, 123.4, 119.8, 108.8, 93.3, 75.2 (s, *J* 27.8 Hz), 26.5, 21.2 ppm; FT-IR (ATR) ν_{\max} : 2923, 2854, 1735, 1616, 1465, 1369, 1222, 1076, 1022, 968, 748 cm⁻¹; GC/MS (EI) *m/z* (%): 175 (16), 133 (59), 165 (100), 166 (10), 207 (22), 297 (M⁺, 0.01); HRMS: calcd. M⁺(-FOH) = 261.1154, found: 261.1154; EA required for C₁₈H₁₆FNO₂: C 72.7, H 5.4, N 4.7%; found: C 72.5, H 5.7, N 4.9%.

Acknowledgements

We gratefully acknowledge financial support from the Spanish Ministerio de Ciencia, Innovación y Universidades (project RED2018-102387-T) the Spanish Ministerio de Economía, Industria y Competitividad, Agencia Estatal de Investigación (AEI) and Fondo Europeo de Desarrollo Regional (FEDER, EU) (projects CTQ2016-76782-P, CTQ2016-80375-P, CTQ2017-82935-P, PID2019-104090RB-100 and PID2019-107268GB-I00), the Generalitat Valenciana (IDIFEDER/2021/013, CIDEAGENT/2020/058 and APOTIP/2020/002), Medalchemy S. L. (Medalchemy-18T) and the University of Alicante (VIGROB-068, UAUSTI21-05). P.M. thanks

the Regional Government of Aragon (Grupos 17R-34 and a pre-doctoral contract to M.P.) for financial support. The authors thankfully acknowledge the resources from the super-computers "Memento" and "Cierzo", technical expertise and assistance provided by BIFI-ZCAM (Universidad de Zaragoza, Spain)

Supplementary Material

Copies of ^1H , ^{19}F and ^{13}C NMR spectra and computational details are provided in the Supplementary Material associated with this paper.

References

1. Khetmalis, Y. M.; Shivani, M.; Murugesan, S.; Sekhar, K. V. G. C. *Biomed. Pharmacotherapy* **2021**, *141*, 111842.
<https://doi.org/10.1016/j.biopha.2021.111842>
2. Yamada, Y.; Kitajima, M.; Kogure, N.; Takayama, H. *Tetrahedron* **2008**, *64*, 7690-7694.
<https://doi.org/10.1016/j.tet.2008.06.030>
3. Reisman, S. E.; Ready, J. M.; Weiss, M. M.; Hasuoka, A.; Hirata, M.; Tamaki, K.; Ovaska, T. V.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 2087-2100.
<https://doi.org/10.1021/ja076663z>
4. Kulkarni, M. G.; Dhondge, A. P.; Chavhan, S. W.; Borhade, A. S.; Shaikh, Y. B.; Bihade, D. R.; Desai, M. P.; Dhatrik, N. R. *Beilstein J. Org. Chem.* **2010**, *6*, 876-879.
<https://doi.org/10.3762/bjoc.6.103>
5. Figueiredo, G. S. M.; Zardo, R. S.; Silva, B. V.; Violante, F. A.; Pinto, A. C.; Fernandes, P. D. *Pharmacol. Biochem. Behaviour* **2013**, *103*, 431-439.
<https://doi.org/10.1016/j.pbb.2012.09.023>
6. Kagata, T.; Saito, S.; Shigermori, H.; Ohsaki, A.; Ishiyama, H.; Kubota, T.; Kobayashi, J. *J. Nat. Prod.* **2006**, *69*, 1517-1521.
<https://doi.org/10.1021/np0602968>
7. Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432-2506.
<https://doi.org/10.1021/cr4002879>
8. Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013-1029.
<https://doi.org/10.1016/j.jfluchem.2006.06.007>
9. Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359-4369.
<https://doi.org/10.1021/jm800219f>
10. Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320-330.
<https://doi.org/10.1039/B610213C>
11. Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637-634.
<https://doi.org/10.1002/cbic.200301023>
12. Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881-1886.
<https://DOI: 10.1126/science.11319>
13. Gillman, K.; Bocchino, D. M. **2004**, *Carbohydrate prodrugs of fluorooxindoles* US Patent: 6 916 937.
14. Liu, Y.-L.; Wang, X. P.; Wei, J.; Li, Y. *Org. Biomol. Chem.* **2022**, *20*, 538-552.
<https://doi.org/10.1039/d1ob01964c>

15. Gu, X.; Zhang, Y.; Xu, Z.-J.; Che, C.-M. *Chem. Commun.* **2014**, 50, 7870-7873.
<https://doi.org/10.1039/C4CC01631A>
16. Li, J.; Cai, Y.; Chen, W.; Liu, X.; Lin, L.; Feng, X. *J. Org. Chem.* **2012**, 77, 9148-9155.
<https://doi.org/10.1021/jo301705t>
17. Deng, Q.-H.; Wadepohl, H.; Gade, L. H. *Chem. Eur. J.* **2011**, 17, 14922-14928.
<https://doi.org/10.1002/chem.201102375>
18. Shen, K.; Liu, X. H.; Lin, L. L.; Feng, X. M. *Chem. Sci.* **2012**, 3, 327-334, and references cited therein.
<https://doi.org/10.1039/C1SC00544H>
19. Hewawasam, P.; Gribkoff, V. K.; Pendri, Y.; Dworetzky, S. I.; Meanwell, N. A.; Martínez, E.; Boissard, C. G.; Post-Munson, D. J.; Trojnacki, J. T.; Yeleswaram, K.; Pajor, L. M.; Knipe, J.; Gao, Q.; Perrone, R.; Starrett, J. E. *Bioorg. Med. Chem. Lett.* **2002**, 12, 1023-1026.
[https://doi.org/10.1016/S0960-894X\(02\)00101-4](https://doi.org/10.1016/S0960-894X(02)00101-4)
20. Dou, X.; Lu, Y. *Org. Biomol. Chem.* **2013**, 11, 5217-5221.
<https://doi.org/10.1039/C3OB41267A>
21. Wang, T.; Hoon, D. L.; Lu, Y. *Chem. Commun.* **2015**, 51, 10186-10189.
<https://doi.org/10.1039/C5CC03289J>
22. Kim, Y. S.; Kwon, S. J.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2015**, 36, 1512-1515.
<https://doi.org/10.1002/bkcs.10263>
23. Balaraman, K.; Ding, R.; Wolf, C. *Adv. Synth. Catal.* **2017**, 359, 4165-4169.
<https://doi.org/10.1002/adsc.201701107>
24. Balaraman, K.; Wolf, C. *Angew. Chem., Int. Ed.* **2017**, 56, 1390-1395.
<https://doi.org/10.1002/anie.201608752>
25. Xie, C.; Zhang, L.; Sha, W.; Soloshonok, V. A.; Han, J.; Pan, Y. *Org. Lett.* **2016**, 18, 3270-3273.
<https://doi.org/10.1021/acs.orglett.6b01516>
26. Xie, C.; Zhang, L.; Mei, H.; Han, J.; Soloshonok, W. A.; Pan, Y. *Chem. Select* **2016**, 1, 4435-4439.
<https://doi.org/10.1002/slct.201601197>
27. Xi, C.; Sha, W.; Zhu, Y.; Han, J.; Soloshonok, V. A.; Pan, Y. *RSC Adv.* **2017**, 7, 5679-5683.
<https://doi.org/10.1039/C6RA27710A>
28. Zhu, Y.; Mei, H.; Han, J.; Soloshonok, V. A.; Zhou, J.; Pan, Y. *J. Org. Chem.* **2017**, 82, 13663-13670.
<https://doi.org/10.1021/acs.joc.7b02409>
29. Moskowitz, M.; Balaraman, K.; Wolf, C. *J. Org. Chem.* **2018**, 83, 1661-1666.
<https://doi.org/10.1021/acs.joc.7b03084>
30. Qiu, Z.-B.; Chen, L. Y.; Ji, J.; Ren, X.; Li, Y. *J. Fluorine Chem.* **2020**, 236, 109594.
<https://doi.org/10.1016/j.jfluchem.2020.109594>
31. Zhao, J.-b.; Ren, X.; Zheng, B.-q.; Ji, J.; Qiu, Z.-b.; Li, Y. *J. Fluorine Chem.* **2018**, 215, 44-51.
<https://doi.org/10.1016/j.jfluchem.2018.09.004>
32. Zang, L.; Zhang, W.; Mei, H.; Han, J.; Soloshonok, V. A.; Pan, Y. *Org. Biomol. Chem.* **2017**, 15, 311-315.
<https://doi.org/10.1039/C6OB02454H>
33. For a review, see: Ortega-Martínez, A.; Molina, C.; Moreno-Cabrero, C.; Sansano, J. M.; Nájera, C. *Eur. J. Org. Chem.* **2018**, 2394-2405.
<https://doi.org/10.1002/ejoc.201800063>
34. Molina, C.; Ortega-Martínez, A.; Sansano, J. M.; Nájera, C. *Org. Biomol. Chem.* **2019**, 17, 482-489.

<https://doi.org/10.1039/C8OB01811A>

35. Ortega-Martínez, A.; Molina, C.; Moreno-Cabrerizo, C.; Sansano, J. M.; Nájera, C. *Synthesis* **2017**, *49*, 5203-5210.
<https://doi.org/10.1055/s-0036-1590880>
36. Ortega-Martínez, A.; Molina, C.; Moreno-Cabrerizo, C.; Sansano, J. M.; Nájera, C. *An. Acad. Bras. Cienc.* **2018**, *90-Suppl. 2*, 1089-1099.
<https://doi.org/10.1590/0001-3765201820170783>
37. Moreno-Cabrerizo, C.; Ortega-Martínez, A.; Esteruelas, M. A.; López, A. M.; Nájera, C.; Sansano, J. M. *Eur. J. Org. Chem.* **2020**, 3101–3109.
<https://doi.org/10.1002/ejoc.202000375>

This paper is an open access article distributed under the terms of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>)