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Enantioselective synthesis of 2-ethyl-2,3-dihydrobenzofuran carboxylic acid, direct precursor of (+)-efaroxan, from a Baylis–Hillman adduct

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Abstract—We describe herein a new and straightforward enantioselective approach to *R*-(+)-2-ethyl-2,3-dihydrofuran carboxylic acid, the direct precursor of (+)-efaroxan, an α_2 adrenoreceptor antagonist, which is indicated to be used for the treatment of neurodegenerative diseases (Alzheimer and Parkinson), migraine and type II diabetes. Our goal was accomplished using a Baylis–Hillman adduct as starting material. The dihydrobenzofuran acid was obtained in eight steps with an overall yield of 14%.

It is well known that some imidazoline-containing ligands have an affinity for binding sites distinct from α-adrenoreceptors and two discrete imidazoline receptors (designated I_1 and I_2) are well characterized.[1] Recently, a third imidazoline binding site (putatively designed as I_3) was identified in pancreatic β-cells and this receptor is associated with control of insulin secretion.[2] Insulin secretagogue activity mediated by imidazoline agonists is known to be associated with closure of ATP-sensitive potassium (K_{ATP}) channels, leading to membrane depolarization and Ca^{+2} influx.[3]

Apparently, the biological effects exerted by (*R*)-(+)-efaroxan (**1**, Fig. 1)[4] are directly related to its α_2-adrenoreceptor antagonism, while those demonstrated by its (−)-enantiomer are mediated by the I_3 receptor.[5]

The high pharmacological potentiality of efaroxan (**1**) and derivatives (**3**–**5**) have motivated the development of several approaches to their total syntheses.[6] In most of them, the 2,3-dihydrobenzofuran carboxylic acid (**2**, Fig. 1) has been used as key intermediate.

The biological activities exhibited by efaroxan (1) and also by their derivatives are clearly related to the absolute configuration of the quaternary asymmetric centre. The preparation of efaroxan in its enantiomerically pure form was initially achieved by resolution of racemic **2**.[3,7] Only recently, Imbert and co-workers[8] have described the first successful approach for the preparation of (*R*)-2-ethyl-2,3-dihydrobenzofuran carboxylic acid (**2**).

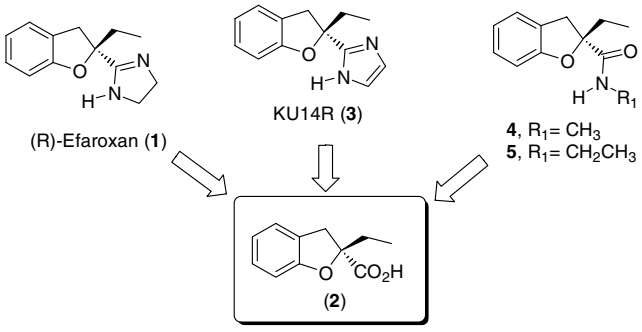

Figure 1. 2-Ethyl-2,3-dihydrobenzofuran **2** as key intermediate to the synthesis of efaroxan and derivatives.

The pharmacological relevance of efaroxan associated with a research program focused on exploiting the synthetic potentiality of the Baylis–Hillman adducts as starting materials for the synthesis of valuable compounds[9] stimulated us to proposing an alternative enantioselective approach for the preparation of the dihydrobenzofuran acid **2**. Our intention was to develop a versatile strategy that could guarantee the access to the

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both enantiomers of **2**, since they both exhibit interesting pharmacological properties.

2-Ethyl-2,3-dihydrobenzofuran carboxylic acid (**2**), in which the absolute stereochemistry of the quaternary centre was already controlled, could be prepared through a base-catalyzed cyclization reaction (via a nucleophilic aromatic substitution reaction) of the chiral fluorinated hydroxyacid **6**, which in turn, could be obtained from epoxyalcohol **7**. A Sharpless asymmetric epoxidation on the α-substituted allylic alcohol **8** could furnish the intermediate epoxy **7**, in its enantiomerically pure form. The preparation of **8** could be assured through a Michael addition of an organocuprate on the terminal double bond of acetylated Baylis–Hillman adduct **9**, following by in situ elimination of an acetate group. A Baylis–Hillman reaction between methyl acrylate and 2-fluorobenzaldehyde followed by an acetylation reaction could secure the formation of **9**, as depicted below (Scheme 1).

Besides the atom efficiency, the success of this strategy could provide convenient access to enantiomerically pure derivatives of efaroxan, simply changing the aldehyde used in the Baylis–Hillman reaction. Use of enantiomeric tartarate in the Sharpless reaction would allow the easy preparation of the minus enantiomers of **2**.

We report herein the sequence, which led to the asymmetric total synthesis of dihydrobenzofuran carboxylic acid **2**.

The Baylis–Hillman reaction[10] between commercial 2-fluorobenzaldehyde and methyl acrylate, in the presence of a catalytic amount of DABCO and ultrasound radiation[11] gave the adduct **10** in 90% yield, after chromatographic purification. A solution of the Baylis–Hillman adduct in dry dichloromethane was treated with acetyl chloride, DMAP and triethylamine to furnish the acetylated derivative (**9**) in 90% yield (Scheme 2). To our surprise, the treatment of **9** with lithium dimethyl cuprate at 0 °C led to the formation of a mixture of two products (**11** and **12**; ratio 3:2), in 40% yield. The olefin **11** was the product required for our strategy. By-product **12** could be formed through a dimerization step, most probably involving the intermediates of the cuprate addition (Scheme 2).[12,13] To overcome the low yield and avoid the formation of **12**, several experimental modifications were tested. In Table 1 we summarize the results achieved for the optimization of cuprate addition reaction.

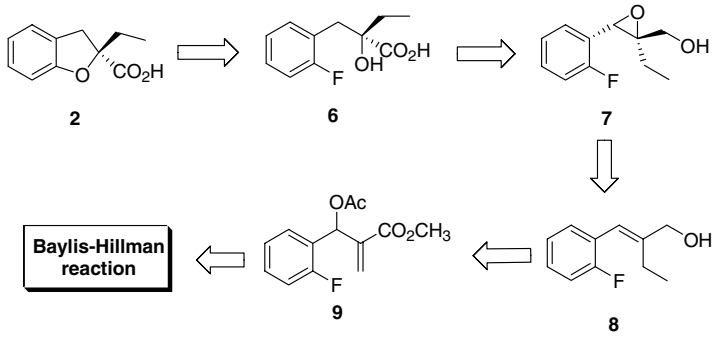
The 1,4 addition of the lithium dimethylcuprate reagent is quite fast as is the formation of the byproduct **12**. At −50 °C, the formation of **12** could be minimized, however it was not possible to completely avoid it. A similar observation has been reported by Ullenius, when she tried to add lithium dimethylcuprate to *ortho*-substituted methyl cinnamates.[14]

The cinnamate derivative **11** was reduced with DIBAL-H, at −78 °C in dichloromethane to furnish the corre-

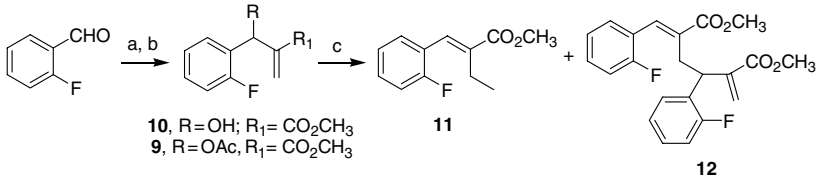
Table 1. Optimization of cuprate 1,4-addition reaction on acetylated Baylis–Hillman adduct **9**

Entry	Temperature (°C)	Time (min)	Ratio product **11**:**12**	Yields (%) **11**/**12**[a,b]
1	0	1	42:58	39/50
2	−20	8	45:55	40/50
3	−30	15	58:42	44/38
4	−50	20	70:30	68/25

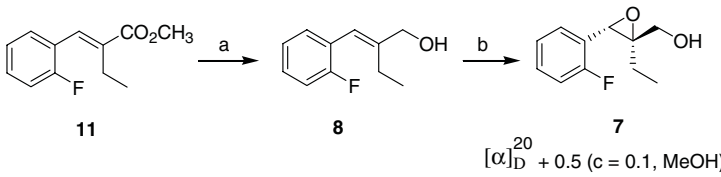
[a] Isolated and purified product.
[b] Fully characterized by ^{1}H, ^{13}C NMR and MS.



Scheme 1. Retrosynthetic analysis for the preparation of **2**.



Scheme 2. Reagents and conditions: (a) methyl acrylate, DABCO, MeOH, ultrasound, 16 h, 90%; (b) acetyl chloride, DMAP, NEt_3, CH_2Cl_2, 12 h, 90%; (c) $Li(CH_3)_2Cu$, diethyl ether, −30 °C, 20 min, 68%.



Scheme 3. Reagents and conditions: (a) DIBAL-H, −78 °C, CH_2Cl_2, 2 h, 85%; (b) L-(+)-DIPT, Ti(*O*–*i*Pr)$_4$, THBP, molecular sieves (4 Å), CH_2Cl_2, −35 °C, 8 h, 75%, 89% ee.

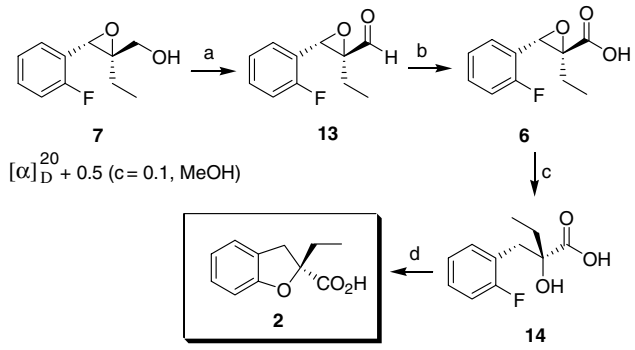
sponding allylic alcohol **8**, in 85% yield, which was used, after purification, as substrate for a Sharpless–Katsuki epoxidation reaction.[15] Unfortunately, the chemical yield of this oxidation reaction was very low (45%, Scheme 3). An additional study was carried out, in which three reaction parameters were varied (molar ratio of titanium isoproxide and tartarate and the temperature of the reaction). The results are summarized in Table 2.

The best yield and reproducibility were attained when diisopropyl tartarate (60 mol %) was used, at −35 °C, with 50 mol % of titanium isopropoxide (entry 5). The epoxide-alcohol **7** was prepared in 75% of yield and 89% ee.

The enantiomeric purity of this epoxide was determined by GC using a chiral column (Chiral HP column—β-cyclodextrin).

At this stage, the stereochemistry of the quaternary carbon was already controlled. Based on the rationalization proposed by Sharpless, the oxygen of the hydroperoxide should be transferred to the *Si* face of the double bond to produce epoxide with (*S*,*S*)-configuration.

We tried to directly oxidize the epoxide-alcohol **7** to the corresponding carboxylic acid **6**, with Jones reagent at 0 °C. However, in our hands the acid was obtained in only 40% yield, with an intense degradation of the reaction medium. Based on a previous experience of our laboratory, we decided first to oxidize the alcohol to an aldehyde and then to the acid, using mild experimental conditions.[16] Treatment of alcohol **7** with TPAP/NMO gave the epoxy-aldehyde **13** in 85% yield.[17] Acid **6** was obtained from aldehyde **13** through treatment with sodium chlorite, NaH_2PO_4 and 2-methyl-2-butene in 90% yield (Scheme 4).[18] Reductive opening of **7** was completely regioselective and gave the α-hydroxy acid



Scheme 4. Reagents and conditions: (a) TPAP, *N*-methyl morfoline-*N*-oxide (NMO), dichloromethane, rt, 1 h, 85%; (b) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, acetone, 0 °C → rt, 4 h, 90%; (c) Pd/C 5%, EtOH, rt, 12 h, 80%; (d) NaH, toluene/DMF (8:2), 110 °C, 16 h, 65%.

14, as the sole isolable product in 80% yield. The cyclization reaction was carried out with NaH in DMF to furnish **2**, in 65% yield (Scheme 4). The diidrobenzofuran ring was formed through a nucleophilic aromatic substitution reaction (S_NAr). In this type of nucleophilic attack fluorine used to be the best leaving group. The most likely explanation is that the first step of the S_NAr mechanism is usually the rate determining, and this step is promoted by groups with strong $-I$ effects. This would explain why fluoro is such a good leaving group when this mechanism is operating.[19]

To confirm the optical purity and the absolute configuration of the dihydrobenzofuran **2** we decided to use the strategy described by Imbert and co-workers.[7] The chiral acid **2** was then treated with an equimolar amount of (*S*)-(+)-2-phenylglycinol in ethyl acetate. The crystalline solid salt was filtered and recrystallized twice in methylethylketone. The solid was dissolved in methanol and its specific rotation was measured {$[\alpha]_D^{20}$ 54.8 (*c* 0.3, MeOH); Lit.[7] $[\alpha]_D^{20}$ 55.9 (*c* 0.3, MeOH)}.

Table 2. Sharpless–Katsuki reaction with allylic alcohol **8**

Entry	Ti(O–*i*Pr)$_4$ (mol %)	Tartarate[a] (mol %)	Temperature (°C)	Time (h)	Yield[b] (%)/% ee[c]
1	100	(+)-DET (100)	−25	12	45/89
2	100	(+)-DET (100)	−25	12	52/89
3	100	(+)-DET (120)	−25	12	58/87
4	100	(+)-DIPT (120)	−35	8	75/89
5	50	(+)-DIPT (60)	−35	8	75/89
6	25	(+)-DIPT (30)	−35	8	70/85

[a] All reactions were carried out in the presence of molecular sieves (4 Å), using 0.5 mmol of allylic alcohol **8**.
[b] The yields are for purified and isolated products.
[c] The enantiomeric purity was determined by GC using a chiral column (using a racemic product for comparison).

Based on these data our product has an optical purity >95% ee. The synthesis of the (*R*)-(+)-2-ethyl-2,3-dihydrobenzofuran carboxylic acid **2** was accomplished in eight steps, from the Baylis–Hillman adduct, with an overall yield of 14%.[20] The utilization of the commercial (−)-DIPT in the place of (+)-DIPT should permit access to the (*S*)-(−)-enantiomer using the same synthetic strategy.[21,22] Our strategy should also permit the preparation of several derivatives of both the enantiomers of efaroxan, substituted in aromatic ring.

Finally this simple and straightforward strategy exemplifies clearly the synthetic potentially of the Baylis–Hillman reaction for the preparation of chiral compounds of pharmaceutical interest.

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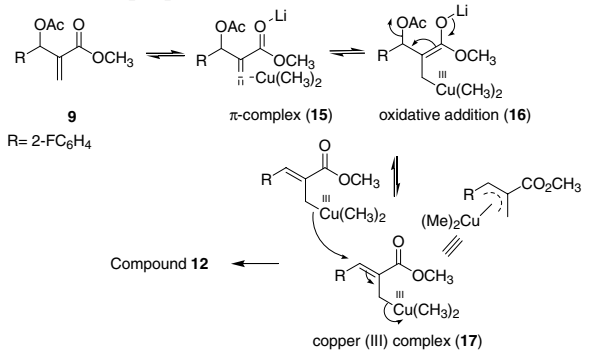
13. There are in the literature some controversies concerning the mechanism of the 1,4-addition of organocuprate reagent on α,β-unsaturated compounds. Based on available theoretical evidences, compound **12** perhaps could be formed as shown below. Further studies should be done to confirm this proposition.



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22. The spectroscopic data (^{1}H, ^{13}C NMR, HRMS) for all intermediates are compatible with the proposed structures. Compound **10**: 80% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.02 (m, 4H), 6.33 (s, 1H). 5.87 (s, 1H), 5.75 (s, 1H), 3.75 (s, 3H), 2.90 (s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.6, 161.4, 158.1, 140.6, 128.1, 127.9, 126.4, 124.1, 115.1, 67.0, 52.0. IR (λ_{max}, film) 3437, 1721 cm^{-1}. HRMS (*m*/*z*) Calcd for $C_{11}H_{11}O_3F$ 210.06922; found 210.06904; Compound **11**: 65% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.4–7.05 (m, 4H), 3.83 (s, 3H), 2.48 (q, $J = 7.4$ Hz, 2H), 1.14 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 167.9, 161.7, 158.4, 136.6, 131.0, 129.8, 123.7, 115.6, 51.9, 30.3, 21.2, 13.7. IR (λ_{max}, film) 1719, 1245 cm^{-1}; HRMS (*m*/*z*) Calcd for $C_{12}H_{13}FO_2$ 208.08995; found 208.09003. Compound **7**: 75% yield; 89% ee (chiral HP column); $[\alpha]_D$ 0.5 (*c* 0.1, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.02 (m, 4H), 4.31 (s, 1H), 3.94 (d, $J = 12.4$ Hz, 1H), 3.80 (d, $J = 12.4$ Hz, 1H), 1.93 (broad s, 1H), 1.55 (qd, $J = 7.5$ Hz, 1H), 1.29 (qd, $J = 7.5$ Hz, 1H), 0.83 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 161.8, 159.8, 128.2, 123.7, 123.2, 129.0, 114.9, 66.6, 62.4, 56.2, 20.9; IR (λ_{max}, film) 3355, 1118 cm^{-1}. HRMS (*m*/*z*) calcd for $C_{11}H_{13}FO_2$ 196.08996; found 196.08978. Compound **12**: 25% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.6 (s, 1H), 7.26 (m, 1H), 7.10 (m, 1H), 7.01 (m, 2H), 6.89 (m, 4H), 6.31 (s, 1H), 5.62 (s, 1H), 4.49 (dd, $J = 9.46$ and 5.8 Hz, 1H), 3.80 (s, 3H), 3.59 (s, 3H), 3.02 (ddd, $J = 13.13$, 9.46 and 5.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 168.6, 161.8, 160.6, 159.9, 158.7, 141.6, 134.14, 132.8, 129.9, 128.9, 128.1, 128.0, 125.2, 123.7, 115.5, 115.3, 52.0, 51.7, 37.9, 31.2; IR (λ_{max}, film) 1689, 1672 cm^{-1}; HRMS (*m*/*z*) calcd for $C_{23}H_{22}F_2O_4$ 400.14862; found 400.14848. Compound **13**: 85% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.1 (s, 1H), 7.40–7.05 (m, 4H), 4.5 (s, 1H), 2.85 (m, 1H), 1.88 (m, 1H), 0.95 (t, $J = 6.9$ Hz, 3H); IR (λ_{max}, film) 2800, 1750 cm^{-1}; HRMS (*m*/*z*) Calcd for $C_{11}H_{11}FO_2$ 194.07431; found 194.07401. Compound **2**: 65% yield; {$[\alpha]_D^{20}$ 54.8 (*c* 0.3, MeOH); Lit.[7] $[\alpha]_D^{20}$ 55.9 (*c* 0.3, MeOH)—(*S*)-phenylglycinol salt}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5–7.30 (m, 2H), 7.19–7.08 (m, 2H), 3.71 (d, $J = 16.5$ Hz, 1H), 3.43 (d, $J = 16.5$ Hz, 1H), 2.29 (m, $J = 7.3$ Hz, 2H), 1.25 (t, $J = 7.3$ Hz, 3H). IR (λ_{max}, KBr): 1728 cm^{-1}.