Selectivity in aromatic fluorination. Introduction of fluorine probes into nabilone

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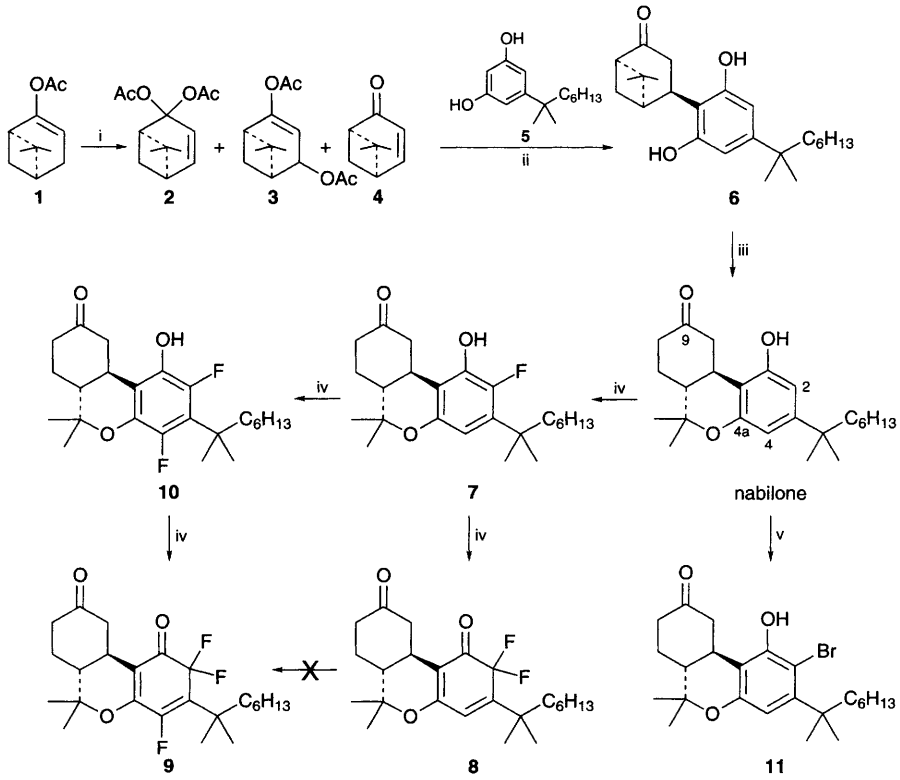
Selective fluorination of the aromatic ring of nabilone leads to functional analogues with diminished affinity for the CB1 receptor, thereby confirming the hypothesis that the phenolic hydroxy group is engaged in a hydrogen bonding interaction with the receptor.

The identification of two distinct cannabinoid receptors[1] and the recent discovery of an endogenous ligand[2] has stimulated interest in the use of cannabinoids for therapeutic purposes. A more detailed understanding of the receptor–ligand interactions would facilitate specific ligand design. The antinauseant drug nabilone[3] structurally resembles the natural cannabinoids, and incorporates the following features which are known to potentiate activity: a phenolic hydroxy group at C(1), a lipophilic sidechain at C(3), and a polar group at C(9).[4] The phenolic hydroxy group is known to be an important determinant of the activity in both the classical and the non-classical cannabinoid series, suggesting that a hydrogen-bonding interaction with the receptor may be taking place. Placement of a fluorine atom adjacent to the phenolic hydroxy group will affect the strength of this hydrogen bond.

During the execution of this work, an improved synthesis of nabilone was developed (Scheme 1). Enol acetate **1**, derived from (+)-nopinone,[3] was oxidized with $Pb(OAc)_4$ to produce a 65 : 30 : 5 mixture of diacetates **2** and **3** and enone **4**. The yield was nearly quantitative at all scales at which the reaction was carried out (1–20 g of **1**). Attempts to purify the product mixture by vacuum distillation, according to the published procedure,[3] led to sharply diminished yields of **2** and **3**.† Treatment of the crude reaction mixture of **2**, **3** and **4** with resorcinol **5** and aq. TsOH in $CHCl_3$ at room temperature[3] led to **6** in 76% overall yield. Purification was accomplished by recrystallization from CH_2Cl_2–EtOAc–hexanes (1 : 1 : 20). Rearrangement–cyclization of **6** to nabilone took place in 98% yield in $MeNO_2$ at 0 °C in the presence of trimethylsilyl triflate.‡ These modifications to the earlier work[3] result in a much higher overall yield of nabilone from **1** (74 *vs.* 24%).

Attention was focused on the introduction of the aromatic fluorine. The reaction of XeF_2 with nabilone led to a mixture of fluorinated products, along with unreacted nabilone.[5] Efforts to optimize the process were unsuccessful. Exposure of nabilone to 1 equiv. of *N*-fluoropyridinium triflate in CH_2Cl_2 at room temperature for 1 d led to 2-fluoronabilone **7** in 88% yield.[6]§ No other fluorine-containing products could be detected by ^{19}F NMR. The ease of this reaction, the high yield, as well as the absence of protecting group for the ketone, recommend its use.



Scheme 1 *Reagents and conditions*: i, $Pb(OAc)_4$, PhH, gentle reflux, 2 h; ii, aq TsOH, $CHCl_3$, room temp. 1 d; iii, CH_3NO_2, Me_3SiOTf, 0 °C to room temp., 5 h; iv, *N*-fluoropyridinium triflate, CH_2Cl2; v, Br_2, HOAc, NaOAc, room temp.

That fluorination had taken place *ortho* to the phenolic hydroxy group, rather than *para*, was ascertained from the following evidence: (1) The aryl hydrogen (δ 6.23) shows a correlation to C(4a) in the HMBC spectrum. This correlation would only be observed if the aryl hydrogen were at C(4). (2) No NOE correlation was observed between the phenolic hydroxy group proton and the aryl hydrogen in the 300 MHz ^{1}H NMR spectrum. In the cannabinoid series, *ortho* hydrogen invariably shows a NOE correlation to the phenol OH. (3) The phenolic OH appears as a doublet with 8.4 Hz coupling constant to fluorine in the ^{1}H NMR spectrum. No such coupling would be observed for 4-fluoronabilone.

Exposure of nabilone to an excess of *N*-fluoropyridinium triflate at 90 °C in a sealed tube led to a 3 : 1 mixture of fluorides **8** and **9** in *ca.* 80% yield.§ The balance of the material was present as monofluoride **7**. Further treatment of the mixture of **8** and **9** with *N*-fluoropyridinium triflate led to no change in product composition, indicating that **8** was not being converted to **9** under the reaction conditions. Therefore, it is likely that **7** was first converted to 2,4-difluoronabilone **10** on the way to **9**. Furthermore, the relative proportion of **8** and **9** suggests that the transformation of **7** to difluorocyclohexadienone **8**, a process in which the aromaticity of the ring is lost, takes place more rapidly than the substitution reaction which leads to **10**. It is likely that both **8** and **10** share a common (radical) intermediate. Under the forcing reaction condition which was used, no **10** was detected in the product. It may be possible to intercept this intermediate by using smaller excesses of reagent and/or lower reaction temperature.

Direct substitution of nabilone by halogens other than fluorine is unexpectedly difficult, due to the bulk of the C(3) dimethylheptyl group. Several standard reaction conditions for the bromination of phenols failed to convert nabilone to **11**.¶ A modest yield of **11** (38%) was obtained by exposure of nabilone to bromine in acetic acid buffered with sodium acetate. The attenuated electrophilic reactivity of the aromatic ring in nabilone is in sharp contrast with the ease of aromatic halogenation of activated phenols.

The halogenated nabilone derivatives were tested for their affinities for the CB1 cannabinoid receptor.[7] Halogen substitution on the aromatic ring of nabilone invariably results in decreased affinity for the [^{3}H]-CP-55 940 binding site. Thus **11** has a K_i = 14.0 nM, compared to a K_i = 3.0 nM for nabilone, while **7** has an even lower affinity, K_i = 40 nM. The most dramatic effect is observed for the 2,2,4-trifluoro analogue **9**, K_i = 6159 nM, in which the phenolic group of the parent molecule has been replaced by a ketone carbonyl.

An effective method for the introduction of fluorine into nabilone has been described. The reactions leading to the di- and tri-fluorinated derivatives are of interest in a broader context. The receptor binding data confirm that the phenolic hydroxy is an absolute requirement for activity, and also the hypothesis that the phenolic hydroxy group of nabilone is engaged in an acceptor hydrogen bonding interaction with the receptor.

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Footnotes

† Archer and co-workers report a 41% yield of **2** if the reaction mixture was refluxed for 2 h, or a 39% yield of **3** if reflux was maintained for 18 h.[3]

‡ A solution of 259 mg (0.695 mmol) of **6** in 55 ml nitromethane was treated with 2.1 ml (1.04 mmol) of TMSOTf at 0 °C, then stirred at room temp. for 5 h. The reaction was quenched with ice cold aq. $NaHCO_3$, diluted with brine and extracted three times with EtOAc–hexanes (4 : 1). The product was dried ($MgSO_4$), filtered through a short pad of Celite and silica gel. Solvent evaporation led to 255 mg (98% yield) of pure nabilone: $[\alpha]^{20}_D$ −54.5 (*c* 1, $CHCl_3$); lit.,[3] $[\alpha]^{20}_D$ −52.3 (*c* 1, $CHCl_3$). These reaction conditions were first developed by Dr Jakob Busch-Petersen.

§ A solution of 100 mg (0.27 mmol) nabilone in 3.8 ml CH_2Cl_2 was treated with 66 mg (0.27 mmol) *N*-fluoropyridinium triflate at room temp. for 1 d. The solution was diluted with CH_2Cl_2 and washed with sat. aq. $NaHCO_3$. The aqueous phase was extracted twice with CH_2Cl_2. The organic extracts were dried ($MgSO_4$) and evaporated. Silica gel chromatography (15% EtOAc in hexanes) afforded 91 mg (88% yield) of 2-fluoronabilone **7** as a clear oil: $[\alpha]^{21}_D$ −53.3 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23 (d, *J* 7.2 Hz, 1 H), 5.49 (d, *J* 8.4 Hz, exchangeable with D_2O, 1 H), 3.86 (dq, *J* 15.3, 2.1 Hz, 1 H), 2.90 (td, *J* 12.3, 3.6 1 H), 2.60 (dm, *J* 15.3 Hz, 1 H), 2.43 (td, *J* 12.6, 6.9 Hz, 1 H), 2.17 (t, *J* 14.1 Hz, 1 H), 2.20–2.10 (m, 1 H), 1.93 (td, *J* 12.0, 2.7 Hz, 1 H), 1.75–1.40 (m, 3 H), 1.46 (s, 3 H), 1.28 (s, 6 H), 1.11 (s, 3 H), 1.30–1.00 (m, 8 H) and 0.84 (t, *J* 6.9 Hz, 3 H); ^{19}F NMR (283 MHz, $CDCl_3$) δ −149.6 (br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.8, 148.9, 144.8 (d, *J* 228.7 Hz), 142.6, 135.4 (d, *J* 12.0 Hz), 109.7, 107.1 (d, *J* 5.2 Hz), 76.5, 47.0, 45.0, 41.9 (d, *J* 5.2 Hz), 40.8, 37.6 (d, *J* 3.4 Hz), 34.8, 31.7, 29.9, 28.0, 27.8, 26.6, 24.9, 22.6, 18.8 and 14.1; IR (neat) ν_{max}/cm^{-1} 3300, 2960, 2930, 2860, 1710, 1630, 1580, 1495, 1440, 1390, 1380, 1360, 1340, 1260, 1245, 1205, 1190, 1150, 1120, 1100, 1070, 1020, 1005, 970, 940, 880, 850, 810 and 770; EI mass spectrum (*m/z*) 390 (M^+), 375, 357, 334, 305 (100%), 237, 195, 83 and 69; HRMS: calc. for $C_{24}H_{35}O_3F$ (M^+) 390.2570, found 390.2574. **8**: ^{19}F NMR (283 MHz, $CDCl_3$) δ −108.3 (d, *J* 335.7 Hz) and −100.8 (d, *J* 335.7 Hz); HRMS: calc. for $C_{24}H_{34}O_3F_2$ (M^+) 408.2476, found 408.2472. **9**: ^{19}F NMR (283 MHz, $CDCl_3$) δ −118.2 (t, *J* 16.2 Hz), −102.7 (dd, *J* 336.4, 13.0 Hz) and −97.4 (dd, *J* 336.3, 12.3 Hz); HRMS: calc. for $C_{24}H_{33}O_3F_3$ (M^+) 426.2382, found 426.2398.

¶ For example, NBS or KBr/MCPBA/18-C-6 failed to brominate nabilone.

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