Synthesis of a bifunctional cannabinoid ligand

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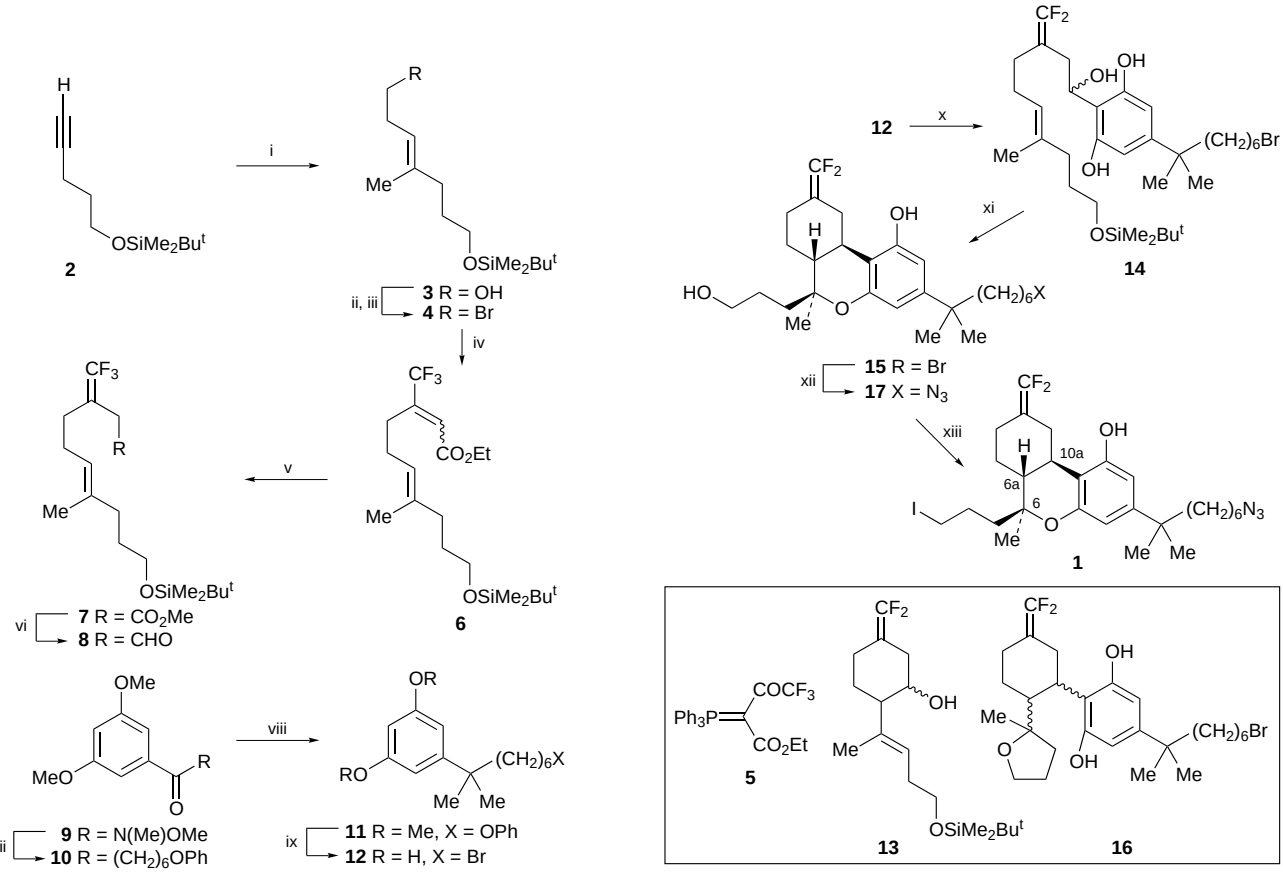
A novel bifunctional classical-nonclassical hybrid cannabinoid has been prepared expeditiously through the Diels–Alder reaction of an *ortho*-quinomethane.

The identification of two distinct cannabinoid receptors[1] has led to a resurgence of interest in this area. Rational design of new materials for pharmaceutical development requires a detailed understanding of receptor–ligand interactions at the molecular level. The availability of cloned cannabinoid CB1 receptor and our identification of a class of high-affinity ligands suggested an experiment in which irreversible covalent binding[2] of the ligand to the receptor at two sites would take place. Partial digestion of the receptor–ligand covalent complex, followed by analysis of the fragments, would serve to locate the ligand within the active site.

A convergent synthesis of the racemate of classical-nonclassical cannabinoid **1** (Scheme 1) is described. The C7′ azido group in **1** can be activated photochemically, whereas the iodo group is expected to react with proximal nucleophilic residues within the active site. In earlier work we have shown that the β-3-iodopropyl group at C6 confers improved binding properties of ligands to the CB1 receptor.[3]

The aliphatic portion of **1** was prepared from the *tert*-butyldimethylsilyl ether of pent-4-yn-1-ol **2** *via* a carboalumination–alkylation process (Scheme 1).[4] Published procedures call for evaporation of the halogenated solvent and its replacement by Et_2O prior to the formation of the alanate. This works well, but is inconvenient on a large scale. We have determined that solvent replacement is unnecessary. Slow addition of a precooled solution of *n*-butyllithium in hexane to the intermediate alane derived from **2** in either $ClCH_2CH_2Cl$ or CH_2Cl_2 at −78 °C produced the alanate.[5] Quenching with ethylene oxide gave alcohol **3** in 88% yield. This represents a significant improvement for the process.

Bromide **4** was obtained from **3** *via* the toluene-*p*-sulfonate following treatment with LiBr. Metal–halogen exchange, addition of the lithio species to phosphorane **5**[6] and treatment with acetic acid gave α,β-unsaturated ester **6**. Exposure of **6** to



Scheme 1 *Reagents and conditions*: i, Cp_2ZrCl_2, $AlMe_3$, CH_2Cl_2, 0 °C, 16 h; Bu^nLi, −45 °C, 0.5 h; ethylene oxide, −30 to 0 °C, 4 h, 88%; ii, TsCl, pyridine, 0 °C; iii, LiBr, acetone, room temp., 82% from **2**; iv, Bu^tLi, Et_2O, −78 °C; **5**, THF, −78 to −14 °C, 16 h; AcOH, 0 °C, 0.5 h, 74%; v, Mg, MeOH, room temp., 16 h; vi, DIBAL-H, Et_2O, −78 °C, 3 h; EtOH, −78 °C, 91% from **6**; vii, $Li(CH_2)_6OPh$, THF, −78 °C, 62%; viii, $TiCl_4$, $ZnMe_2$, CH_2Cl_2, −30 °C to room temp., 4 h; ix, BBr_3, CH_2Cl_2, −78 °C to room temp., 84% from **10**; x, MeMgBr, Et_2O, 0 °C, 1 h; $MgBr_2$, **8**, CH_2Cl_2, −78 °C to room temp.; xi, Tf_2NH, $ZnCl_2$, toluene, reflux, 4 h; Tf_2NH, $ZnCl_2$, MeOH, reflux, 4 h, 38% from **8**; xii, $TMGN_3$, $MeNO_2$, 50 °C, 3 h; xiii, I_2, PPh_3, imidazole, PhH, 35 °C, 0.75 h, 69% from **15**

Mg in MeOH led to difluoromethylene compound **7**, the desired product of fluoride elimination from a β-anionic intermediate. Small amounts (5–7%) of the saturated, β-trifluoromethyl ester were also obtained. Reduction of **7** with DIBAL-H led to aldehyde **8**.

The aromatic portion of **1** was prepared from the Weinreb amide **9** of 3,5-dimethoxybenzoic acid. Reaction of **9** with 6-phenoxyhexyllithium gave phenone **10**. Treatment of **10** with $TiCl_4$ and $ZnMe_2$ introduced the benzylic *gem*-dimethyl grouping in nearly quantitative yield.[7] Subsequent exposure of **11** to BBr_3 in CH_2Cl_2 cleaved all three ether groups and introduced the C7′ bromide of **12**. The overall yield of **12** from **10** was 84%. This protocol represents a significant improvement in terms of total number of steps and convenience over the established synthesis of the 5-(1′,1′-dimethylheptyl)resorcinol moiety.[8,9]

The coupling of **12** to **8** was challenging. Attempts to effect the reaction under Lewis acid catalysis led primarily to **13**, from the intramolecular ene reaction of **8**. Success was realized when resorcinol **12** was first converted to the monobromomagnesium salt, and then treated with a deficiency of aldehyde **8** in the presence of catalytic $MgBr_2$ to produce the coupled material **14** in 53% yield.[10] Unreacted **12** was recycled. Exposure of **14** to toluene-sulfonic acid (TsOH) in MeOH at reflux[11] gave a modest yield of dihydrobenzopyran **15** accompanied by larger amounts of tetrahydrofuran **16**.† The tetrahydrofuran probably results from a stepwise, ionic process.

The cyclization to **15** took place upon treatment of **14** with bis(trifluoromethylsulfonyl)amine[12] and $ZnCl_2$, first in toluene and then in MeOH. The relative stereochemistry at C6, C6a and C10a was determined by NOE experiments in conjunction with HMQC and HMBC experiments. The observed stereochemistry could not have been predicted with confidence from the outset. Cyclization to form the C9 methyl cannabinoid skeleton is known from precedent[11] to produce the C6a–C10a *trans* stereoisomer. Our own work[13] has shown that cyclization to form the Δ^9 unsaturated series produces the unnatural C6a–C10a *cis* stereoisomer as the exclusive product, therefore the stereochemical outcome of the cyclization is easily perturbed by minor structural changes in the *seco* precursor (*cf.* **14**).

The conversion of **14** to **15** is also noteworthy because it provides the strongest support to date for the mechanism, which is postulated to involve formation of a transient *ortho*-quinomethane which undergoes intramolecular hetero-Diels–Alder cycloaddition. Product **15** provides the first example of a Diels–Alder cyclization to a cannabinoid with a stereogenic C6 carbon atom. The fact that only the β-3-hydroxypropyl isomer was formed is consistent with a concerted cycloaddition proceeding through an *exo* transition state. A stepwise ionic process would have led to diastereoisomers at C6.[14] All earlier examples of this reaction led to cannabinoids with a *gem*-dimethyl group at C6.

The conversion of **15** to C7′ azido derivative **17** was effected with tetramethylguanidinium azide ($TMGN_3$).[15] Treatment of the crude reaction product with PPh_3–I_2 complex in the presence of imidazole[16] gave **1** in 69% overall yield from **15**.‡ It is critical that an excess (*ca.* 20 mol%) of I_2 over PPh_3 be used so as to suppress the Staudinger reaction of the phosphine with the azide. It is significant that no protecting groups were used during the execution of these steps. The enantiomers of **1** were easily separated by chiral HPLC.

The methodology which has been outlined in Scheme 1 is currently being applied to the synthesis of a series of cannabinoid ligands. Full experimental details of this work, as well as the receptor binding properties of the products, will be reported in due course.

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Footnotes and References

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† The stereochemistry of **16** was not determined.

‡ *Selected data* for (−)-**1**: $[\alpha]_D$ −14 (*c* 3.0, $CHCl_3$); δ_H ($CDCl_3$, 500 MHz) 6.32 (d, *J* 1.9, 1 H), 6.19 (d, *J* 1.9, 1 H), 4.77 (br s, 1 H), 3.93 (br d, 1 H), 3.32–3.21 (m, 2 H), 3.22 (t, *J* 6.9, 2 H), 2.61 (br d, *J* 13.1, 1 H), 2.50 (td, *J* 11.4, 3.2, 1 H), 2.14–2.06 (m, 1 H), 2.05–1.97 (m, 1 H), 1.91–1.86 (m, 2 H), 1.78–1.73 (m, 2 H), 1.60 (td, *J* 11.4, 2.2, 1 H), 1.56–1.48 (m, 4 H), 1.38–1.28 (m, 3 H), 1.25–1.20 (m, 3 H), 1.20 (s, 6 H), 1.14–1.04 (m, 2 H), 1.06 (s, 3 H); δ_C ($CDCl_3$, 125 MHz) 154.65, 154.42, 151.33 (t, *J* 280), 150.21, 108.52, 107.89, 105.38, 87.12 (t, *J* 18), 77.59, 51.49, 45.69, 44.14, 40.69, 37.30, 35.08 (t, *J* 3), 29.70, 28.77, 28.69, 28.67, 28.22 (t, *J* 2), 27.08 (t, *J* 2), 27.00, 26.52, 24.41, 24.17 (t, *J* 2), 18.38, 7.60; δ_F ($CDCl_3$, 376 MHz) −97.71 (part of AB quartet, *J* 58), −97.87 (part of AB quartet, *J* 58); ν_{max} (neat)/cm^{-1} 3650–3100 (broad), 2960, 2920, 2100, 1760, 1625, 1575, 1415, 1260, 1050; *m*/*z* 601 (M^+, 37%), 476 (100), 456 (30), 128 (39), 127 (26). Calc. for $C_{27}H_{38}F_2IN_3O_3$: 601.1977. Found: 601.1988. Chiral HPLC (1 × 25 cm, Chiracel OD column; 5% Pr^iOH in hexane; 1.75 ml min^{-1}; UV detection at 254 nm) retention time: 29.9 min. Retention time for (+)-**1**: 33.7 min.

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