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A novel methodology for the synthesis of 1-desoxy-Δ^8-tetrahydrocannabinol (THC) analogues

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Abstract—A versatile and efficient sequence was developed for the synthesis of 1-desoxy-Δ^8-THC analogues and is demonstrated by the synthesis of sulfonamide analogues with an acetylene group at the C-2′ position in the side chain. In this procedure the 1-desoxy-Δ^8- THC ring structure is built first and the synthesis of the side chain is then developed.

It is well known in cannabinoid research that the presence of a hydroxyl group at C-1 in tetrahydrocannabinols (THCs) is a prerequisite for biological activity and plays a very important role in its interaction with the CB1 receptors.[1–7] The loss of activity found in 1-methoxy[7] and 1-desoxy-Δ^8-THCs[8] is in agreement with this. However, since the discovery of the cannabinoid CB2 receptors which are peripherally active, and the finding that 1-desoxy-Δ^8-THC-DMH (dimethylheptyl analogue of 1-desoxy-Δ^8-THC)[9] binds potently to CB2 receptors and retains the cannabinoid profile in animal tests, there has been a great deal of interest in the synthesis of 1-desoxy-Δ^8-THCs.

The current method used for their synthesis[9–11] involves the preparation of the Δ^8-THCs with the appropriate side chain first, then by the deoxygenation of the phenolic group at C-1. This is achieved by conversion of the hydroxyl group in the THCs to either its phosphate[8,10,11] (diethylchlorophosphate/DMF) or the phenyl ether[12a] (bromobenzene/pyridine/Cu powder/K_2CO_3) derivative, followed by treatment with Li/liquid ammonia reduction. Unfortunately, the use of dissolving metal reduction step in these procedures limits its utility for the synthesis of desoxy-THCs with side chains carrying reducible functionalities. Another approach[12b] uses as a first step, the synthesis of mono-desoxy-cannabidiol, which is then ring closed to give the known[12a] 1-desoxy-Δ^9-THC. In an effort to synthesize 1-desoxy-Δ^8-THC sulfonamide analogues with an acetylene group at C-2′ position in the side chain, **14** and **15** (Scheme 1), we have developed a versatile and efficient methodology for the synthesis of 1-desoxy-Δ^8-THCs. Briefly, the 1-desoxy-Δ^8-THC ring structure is built first and the synthesis of the side chain is then developed.

The target compounds were synthesized as shown in Scheme 1. The condensation of the synthon *cis*-*p*-menth-2-ene-1,8-diol (**1**)[13a] with resorcinol (**2**) formed the abnormal Δ^8-THC (**3**) as the major product and was isolated by chromatography (ethyl acetate/hexanes) in 54% yield.[13b] This is in contrast to the formation of this product in 32% yield using the synthon *cis*/*trans* *p*-menthadien-2,8-1-ol reported by Petrzilka et al.[14] This key reaction step constructed the 1-desoxy-Δ^8-THC ring structure directly, without having to deoxygenate the 1-phenolic group. Furthermore, the presence of a phenol at C-3 in compound **3** provided a suitable handle, via its triflate derivative **4**, to introduce a variety of side chains at this position by taking advantage of the powerful transition metal mediated cross-coupling reactions with triflates.[15] Thus, the phenol **3** was converted to the triflate **4** using the standard procedure and then treated with Pd catalyzed methoxycarbonylation reaction,[16–18] using a CO balloon, to give the ester **5** in 70% yield. Reduction with $LiAlH_4$ in ether to **6** (90%), followed by conversion of the alcohol to the bromide (PPh_3/CBr_4/CH_2Cl_2) formed **7** (91%). Alkylation[19] with **8** (*n*-BuLi/THF) incorporated the side chain, to give **9**, which was deprotected and subsequently mesylated to form compound **11**. Treatment of the mesylate with NaN_3/DMF

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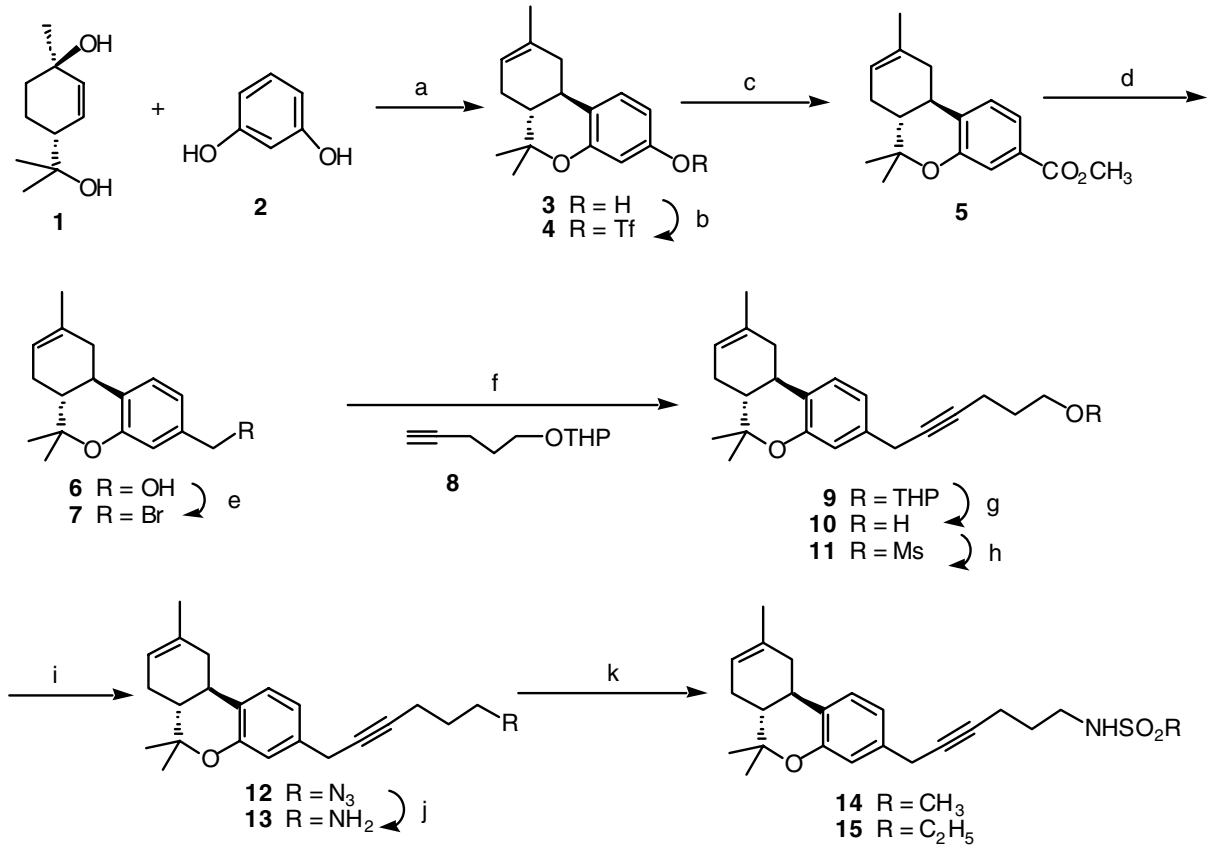

Scheme 1. Reagents and conditions: (a) PTSA, benzene, reflux, 54%; (b) Tf_2O, Py, CH_2Cl_2, 83%; (c) $Pd(OAc)_2$, dppp, CO (1 atm), Et_3N, MeOH, DMF, 70 °C, 70%; (d) $LiAlH_4$, ether, 23 °C, 90%; (e) PPh_3, CBr_4, CH_2Cl_2, 91%; (f) **8**, *n*-BuLi, LiI, THF, reflux; (g) PPTS, MeOH, 84% for the two steps; (h) CH_3SO_2Cl, Et_3N, CH_2Cl_2; (i) NaN_3, DMF, 80% for the two steps; (j) PPh_3, THF–H_2O, 73%; (k) RSO_2Cl, Et_3N, CH_2Cl_2, 73–94%. Overall yield: 9–12%.

converted it to the azide[20] **12**, which was reduced to the amine[20] **13** (PPh_3/THF–H_2O), without isomerization of the acetylene to the allene as an impurity. Target compounds **14** and **15** were formed in 73% and 94% yields, respectively, from **13** using the appropriate sulfonyl chloride[21] ($RSO_2Cl/Et_3N/CH_2Cl_2$). It should be noted that C-1′ benzylic proton in **11** is prone to allene formation. Thus, attempted treatment of the mesylate **11** with methanesulfonamide under basic conditions[22] resulted in inseparable mixtures of the allene and the desired material, under a variety of conditions.

In summary, the present work provides an entry to the synthesis of 1-desoxy-Δ^8-THCs. The procedure is versatile and efficient. Although several steps are involved in the formation of the sulfonamides (11 steps), they are straightforward and the target compounds are formed in overall yields of 9–12%. The sequence is based on a unified and flexible strategy, directly constructing the 1-desoxy-Δ^8-THC ring structure and using the aryl triflate as the key intermediate for the introduction of novel side chains in the molecule. In addition the ester **5** and the bromide **7** offer the possibility of providing a wide variety of novel 1-desoxy-Δ^8-THC analogues. We are currently working on the synthesis of other 1-desoxy-Δ^8-THC analogues with either an acetylene or *cis*-alkene functional group at different positions on the side chain to study structure activity relationships (SAR) in the series. These studies are ongoing and will be reported elsewhere.

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13. (a) Handrick, G. H.; Uliss, D. B.; Dalzell, H. C.; Razdan, R. K. *Tetrahedron Lett.* **1979**, *20*, 681–684; (b) All new compounds were fully characterized. Selected data (NMR recorded in $CDCl_3$ solvent, ^1H at 300 MHz and ^{13}C at 75.6 MHz). (i) **3**: crystals mp 137–138 °C; ^1H NMR: δ 7.06 (d, $J = 8.5$ Hz, 1H), 6.38 (dd, $J = 8.2$, 2.5 Hz, 1H), 6.28 (d, $J = 2.5$ Hz, 1H), 5.46 (s, 1H), 4.52 (s, 1H), 2.60 (m, 2H), 2.13 (m, 1H), 1.93 (m, 1H), 1.82 (m, 1H), 1.73 (s, 3H), 1.68 (m, 1H), 1.37 (s, 3H), 1.14 (s, 3H); ^{13}C NMR: δ 154.8, 154.0, 133.4, 127.6, 119.9, 118.4, 107.6, 103.7, 76.6, 42.8, 36.7, 31.8, 27.6, 27.4, 23.4, 19.1; Anal. calcd $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.88; H, 8.38. (ii) **5**: ^1H NMR: δ 7.50 (dd, $J = 8.0$, 1.4 Hz, 1H), 7.45 (d, $J = 1.4$ Hz, 1H), 7.19 (d, $J = 8.2$ Hz, 1H), 5.41 (s, 1H), 3.82 (s, 3H), 2.60 (m, 2H), 2.10 (d, $J = 15.9$ Hz, 1H), 1.80 (m, 2H), 1.69 (s, 3H), 1.63 (m, 1H), 1.34 (s, 3H), 1.08 (s, 3H); ^{13}C NMR: δ 166.4, 153.0, 132.6, 130.6, 129.0, 126.5, 120.6, 119.7, 118.3, 76.8, 51.5, 42.1, 35.9, 32.2, 27.2, 27.0, 23.1, 18.8. (iii) **6**: ^1H NMR: δ 7.17 (d, $J = 8.0$ Hz, 1H), 6.85 (dd, $J = 8.0$, 1.6 Hz, 1H), 6.77 (d, $J = 1.6$ Hz, 1H), 5.45 (m, 1H), 4.54 (s, 2H), 2.64 (m, 2H), 2.20 (m, 2H), 1.88 (m, 2H), 1.72 (s, 3H), 1.68 (m, 1H), 1.37 (s, 3H), 1.12 (s, 3H); ^{13}C NMR: δ 154.1, 141.4, 134.4, 128.0, 126.0, 121.0, 119.6, 116.8, 78.0, 66.0, 43.8, 37.6, 33.2, 28.6, 28.5, 24.5, 20.1; Anal. calcd $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.99; H, 8.69. (iv) **7**: Colorless oil; ^1H NMR: δ 7.15 (d, $J = 7.7$ Hz, 1H), 6.87 (dd, $J = 7.7$, 1.9 Hz, 1H), 6.81 (d, $J = 1.9$ Hz, 1H), 5.44 (d, $J = 3.0$ Hz, 1H), 4.38 (s, 2H), 2.63 (m, 2H), 2.14 (d, $J = 15.9$ Hz, 1H), 1.76–2.00 (m, 2H), 1.72 (s, 3H), 1.68 (m, 1H), 1.37 (s, 3H), 1.12 (s, 3H); ^{13}C NMR: δ 153.0, 136.7, 133.1, 127.1, 126.0, 120.7, 119.9, 117.6, 77.0, 42.5, 36.3, 33.4, 32.1, 27.5, 27.3, 23.1, 19.1. (v) **14**: ^1H NMR: δ 7.16 (d, $J = 8.0$ Hz, 1H), 6.81 (d, $J = 7.7$ Hz, 1H), 6.78 (s, 1H), 5.46 (s, 1H), 4.34 (m, 1H), 3.49 (s, 2H), 3.29 (m, 2H), 2.94 (s, 3H), 2.65 (m, 2H), 2.34 (m, 2H), 2.15 (m, 1H), 1.6–2.0 (m, 8H), 1.39 (s, 3H), 1.15 (s, 3H); ^{13}C NMR: δ 153.1, 136.4, 133.3, 126.9, 124.0, 119.9, 119.4, 116.4, 80.4, 79.3, 76.6, 42.8, 42.3, 40.2, 36.5, 32.1, 28.8, 27.6, 27.4, 24.6, 23.4, 19.1, 16.1; Anal. calcd $C_{23}H_{31}NSO_3 \bullet 0.4\ C_4H_8O_2$: C, 67.64; H, 7.89; N, 3.21. Found: C, 67.56; H, 7.94; N, 3.32. (vi) **15**: ^1H NMR: δ 7.15 (d, $J = 7.7$ Hz, 1H), 6.81 (d, $J = 7.7$ Hz, 1H), 6.78 (s, 1H),5.46 (s, 1H), 4.46 (m, 1H), 3.48 (s, 2H), 3.25 (m, 2H), 3.04 (m, 2H), 2.65 (m, 2H), 2.33 (m, 2H), 2.16 (m, 1H), 1.6–2.0 (m, 8H), 1.2–1.5 (m, 6H), 1.14 (s, 3H); ^{13}C NMR: δ 153.1, 136.4, 133.3, 126.9, 124.0, 119.9, 119.4, 116.4, 80.5, 79.2, 76.6, 46.8, 42.8, 42.3, 36.6, 32.1, 29.1, 27.6, 27.4, 24.6, 23.4, 19.1, 16.1, 8.31; Anal. calcd $C_{24}H_{33}NSO_3 \bullet 0.7\ C_4H_8O_2$: C, 67.45; H, 8.15; N, 2.93. Found: C, 67.28; H, 7.98; N, 3.20.
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