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Oxaza Adamantyl Cannabinoids. A New Class of Cannabinoid Receptor Probes

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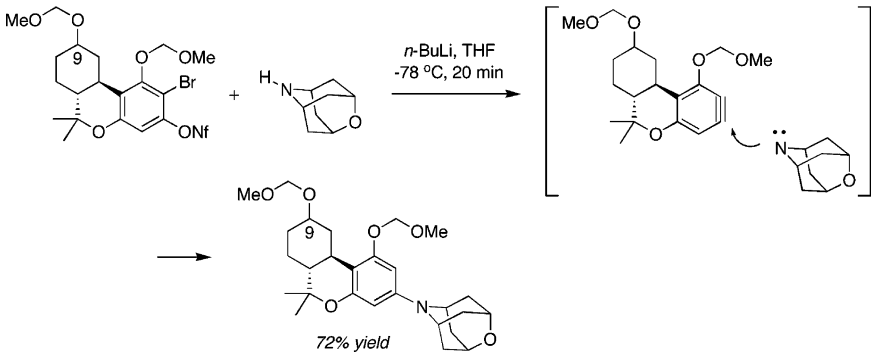

The preparation of C3 oxaza adamantyl cannabinoids has been described starting from phloroglucinol. Straightforward manipulations of the aromatic ring lead to a bromononaflate that is a benzyne precursor and that serves as a common intermediate for the synthesis of diverse C3-substituted tricyclic cannabinoids. Generation of the benzyne in the presence of an oxaza adamantyl amide anion results in efficient and regiospecific addition to C3 of the aromatic ring. This represents an attractive strategy for the synthesis of classical tricyclic cannabinoids that bear a modified aromatic appendage. The oxaza adamantyl cannabinoids that have been prepared represent a new class of ligands for the CB1 and CB2 receptors.

Introduction

The discovery of the two cannabinoid receptors, CB1[1,2] and CB2,[3] ushered in a new era in research into the chemistry and the pharmacology of this class of compounds. Both receptors are membrane-bound and belong to the family of G-protein-coupled receptors (GPCRs). The structural analysis of CB1 and CB2 as well as the study of their interactions with their ligands are hampered by the lack of a crystal structure. Consequently, there is little direct evidence for the mode(s) of interaction between the ligand and receptor.[4] The recognition of CB1 as an important therapeutic target for, inter alia, glaucoma,[5] pain,[6] and appetite modulation[7] indicates a need for a better understanding of the specific interactions between the cannabinoid pharmacophore and the key amino acids associated with the CB1 binding site.

It has long been known that the aliphatic side chain is important for determining the cannabinergic potency of classical tricyclic cannabinoids and also that the presence of a *tert*-alkyl

(1) Devane, W. A.; Dysarz, F. A., III.; Johnson, M. R.; Melvin, L. S.; Howlett, A. C. *Mol. Pharmacol.* **1988**, *34*, 605−613.

(2) Matsuda, L. A.; Lolait, S. J.; Brownstein, M. J.; Young, A. C.; Bonner, T. I. *Nature (London)* **1990**, *346*, 561−564.

(3) Munro, S.; Thomas, K. L.; Abu-Shaar, M. *Nature (London)* **1993**, *365*, 61−65.

(4) For leading references, see: (a) Huffman, J. W.; Miller, J. R. A.; Liddle, J.; Yu, S.; Thomas, B. F.; Wiley, J. L.; Martin, B. R. *Bioorg. Med. Chem.* **2003**, *11*, 1397−1410. (b) Papahatjis, D. P.; Nikas, S. P.; Kourouli, T.; Chari, R.; Xu, W.; Pertwee, R. G.; Makriyannis, A. *J. Med. Chem.* **2003**, *46*, 3221−3229. (c) Papahatjis, D. P.; Nikas, S. P.; Andreou, T.; Makriyannis, A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3583−3586. (d) Khanolkar, A. D.; Lu, D.; Fan, P.; Tian, X.; Makriyannis, A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2119−2124. (e) Huffman, J. W.; Liddle, J.; Duncan, S. G., Jr.; Yu, S.; Martin, B. R.; Wiley, J. L. *Bioorg. Med. Chem.* **1998**, *6*, 2383−2396. (f) Papahatjis, D. P.; Kourouli, T.; Abadji, V.; Goutopoulos, A.; Makriyannis, A. *J. Med. Chem.* **1998**, *41*, 1195−1200. (g) Busch-Petersen, J.; Hill, W. A.; Fan, P.; Khanolkar, A.; Xie, X.-Q.; Tius, M. A.; Makriyannis, A. *J. Med. Chem.* **1996**, *39*, 3790−3796.

(5) (a) Roesch, S.; Ramer, R.; Brune, K.; Hinz, B. *J. Pharm. Exp. Ther.* **2006**, *316*, 1219−1228. (b) Jarvinen, T.; Pate, D. W.; Laine, K. *Pharmacol. Ther.* **2002**, *95*, 203−220.

(6) (a) Huang, S. M.; Walker, J. M. In *Cannabinoids as Therapeutics*; Mechoulam, R., Ed.; Birkhäuser Verlag: Basel, 2005; p 149. (b) Smith, P. F. *Curr. Opin. Invest. Drugs* **2002**, *3*, 859−864.

(7) (a) Barth, F.; Rinaldi-Carmona, M. In *Cannabinoids as Therapeutics*; Mechoulam, R., Ed.; Birkhäuser Verlag: Basel, 2005; p 219. (b) Koch, J. E. *Pharmacol., Biochem. Behav.* **2001**, *68*, 539−543.

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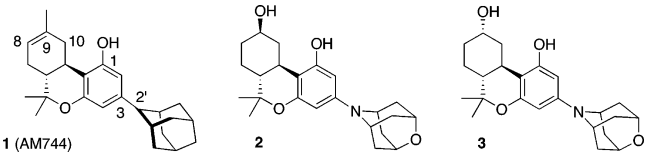
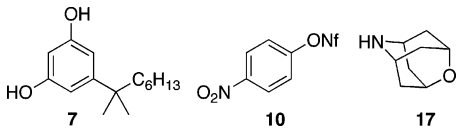


FIGURE 1. Adamantyl and heteroadamantyl cannabinoids.

appendage at C1′ potentiates receptor binding affinity.[8] Nevertheless, it was surprising that cannabinoids bearing a pendant adamantyl group at C3 in place of the *n*-pentyl group that is found in the naturally occurring materials, such as **1** (AM744), were tolerated in both the CB1 and CB2 binding sites.[9] Furthermore, considerable receptor subtype selectivity was observed, depending on the relative orientation of the adamantyl group with respect to the tricyclic nucleus.[9] The ability of the receptor to accommodate the steric bulk of the 1-adamantyl group revealed an unanticipated flexibility and furthermore suggested that introducing heteroatomic functionality on the adamantane structure could be used to interrogate the receptor. Changes in binding affinities of cannabinoids bearing substituted adamantyl residues might indicate the close proximity of polar amino acid residues within the binding pocket. The synthesis of oxaza adamantane **17** has been reported;[10,11] therefore, oxaza adamantyl cannabinoids **2** and **3** (Figure 1) were designed and prepared as the first ligands with which to test this concept. Because the northern aliphatic hydroxyl group is known to be an important pharmacophore, the C9 hydroxyl was incorporated into the structures of **2** and **3**.

Results and Discussion

One of the most attractive approaches to the synthesis of the tricyclic cannabinoid structure is according to the Lilly synthesis of nabilone, whereby a resorcinol is combined with a mixture of diacetates **4** and **5** (see Scheme 1) under acid catalysis.[12] The diacetates are easily derived in two steps from nopinone, the product of ozonolytic cleavage of β-pinene.[13] Minor modifications to this strategy have led to improved overall yields of the condensation product.[14] Although we wanted to retain the advantages of this route, an ancillary goal was the synthesis of an advanced tricyclic intermediate that could be used to prepare a variety of C3-substituted cannabinoids. With this in mind, we condensed diacetates **4** and **5** with phloroglucinol **6**. Whereas condensation of **4** and **5** with resorcinol **7** proceeds in 70% yield, the corresponding process with **6** was more challenging, in large part because of the insolubility of **6** in dichloromethane or chloroform, the preferred solvents for this reaction. After considerable experimentation, we found that exposure of a mixture of **4**, **5**, and **6** in dichloromethane/acetone (4/1, v/v) in the presence of a small excess of *p*-toluenesulfonic acid at room temperature for 20 min led to the desired condensation product **8** in 40% yield. The conversion of **8** to tricyclic cannabinoid **9** was straightforward and took place in 84% yield upon exposure of **8** to $SnCl_4$ in nitromethane.



We assumed that the two phenolic hydroxyl groups at C1 and C3 in **9** could be easily distinguished and that selective functionalization of the more accessible hydroxyl group at C3 would be possible. Our strategy was to first *activate* the C3 hydroxyl toward nucleophilic displacement by nitrogen and then *protect* the C1 hydroxyl. We chose to convert the C3 phenol to the corresponding nonaflate (Nf = $SO_2C_4F_9$). The aryl nonaflates are attractive alternatives to the triflate. They are readily prepared and are more stable toward chromatography or hydrolytic cleavage than the corresponding triflates.[15] The best conditions for the conversion of **9** to nonaflate **11** have been described by Zhu.[16] Treatment of **9** with 4-nitrophenylnonaflate **10** in DMF with CsF at room temperature led to monononaflate **11** in 57% yield. The regiochemical outcome of this reaction was determined by converting **11** to the phenolic acetate and observing an nOe correlation between the axial C10 proton and the acetate methyl group.

Our initial plan had been to use a palladium-catalyzed amination process to form the aryl−nitrogen bond.[17] Although we were successful in coupling the *O*-benzyl ether derivative of **11** with morpholine, our best efforts produced only 15% of the adduct with oxaza adamantane **17**. Fortunately we were able to apply an alternative strategy that promises to be general for the introduction of nitrogen as well as carbon nucleophiles.

The elegant work of Suzuki and co-workers has demonstrated a general approach to the synthesis of substituted benzynes that is summarized in eq 1.[18] Lithium−halogen exchange in **21** leads to elimination of triflate with formation of methoxybenzyne **22**. When this process was carried out in the presence of ketene acetal **23**, [2+2] cycloaddition took place to produce benzocyclobutane **24** in excellent yield. It is noteworthy that this reaction is general and that it produces a single regioisomer of the product. The regioselectivity has been rationalized in terms of

(8) (a) Adams, R. *Harvey Lect.* **1942**, *37*, 168−197. (b) Adams, R.; Harfenist, M.; Loewe, S. *J. Am. Chem. Soc.* **1949**, *71*, 1624−1628.

(9) Lu, D.; Meng, Z.; Thakur, G. A.; Fan, P.; Steed, J.; Tartal, C. L.; Hurst, D. P.; Reggio, P. H.; Deschamps, J. R.; Parrish, D. A.; George, C.; Järbe, T. U. C.; Lamb, R. J.; Makriyannis, A. *J. Med. Chem.* **2005**, *48*, 4576−4585. See also: (a) McLaughlin, P. J.; Lu, D.; Winston, K. M.; Thakur, G.; Swezey, A.; Makriyannis, A.; Salamone, J. D. *Pharmacol., Biochem. Behav.* **2005**, *81*, 78−88. (b) Järbe, T. U. C.; DiPatrizio, N. V.; Lu, D.; Makriyannis, A. *Behav. Pharmacol.* **2004**, *15*, 517−521.

(10) (a) Stetter, H.; Heckel, K. *Tetrahedron Lett.* **1972**, *9*, 801−804. (b) Stetter, H.; Heckel, K. *Chem. Ber.* **1973**, *106*, 339−348.

(11) (a) Portmann, R. E.; Ganter, C. *Helv. Chem. Acta* **1973**, *56*, 1962−1985. (b) Ganter, C.; Portmann, R. E. *Helv. Chem. Acta* **1971**, *54*, 2069−2077.

(12) Archer, R. A.; Blanchard, W. B.; Day, W. A.; Johnson, D. W.; Lavagnino, E. R.; Ryan, C. W.; Baldwin, J. E. *J. Org. Chem.* **1977**, *42*, 2277−2284.

(13) See: Boger, D. L.; Mullican, M. D.; Hellberg, M. R.; Patel, M. *J. Org. Chem.* **1985**, *50*, 1904−1911. **Caution!** As is the case for all ozonolyses, one must be fastidious in destroying all traces of ozonide before concentrating the product. The ozonolysis of β-pinene has resulted in at least one serious accident that was reported in the August 6, 1990, issue of Chemical & Engineering News. It is often the case that the reductive decomposition of ozonides is a relatively slow process when Me_2S is used as the reducing agent, as was the case in the laboratory that reported the accident in 1990. We routinely use thiourea for ozonide decomposition and have experienced no problems with this reaction. The use of thiourea for ozonolysis workups has been described: Gupta, D.; Soman, R.; Dev, S. *Tetrahedron* **1982**, *38*, 3013−3018.

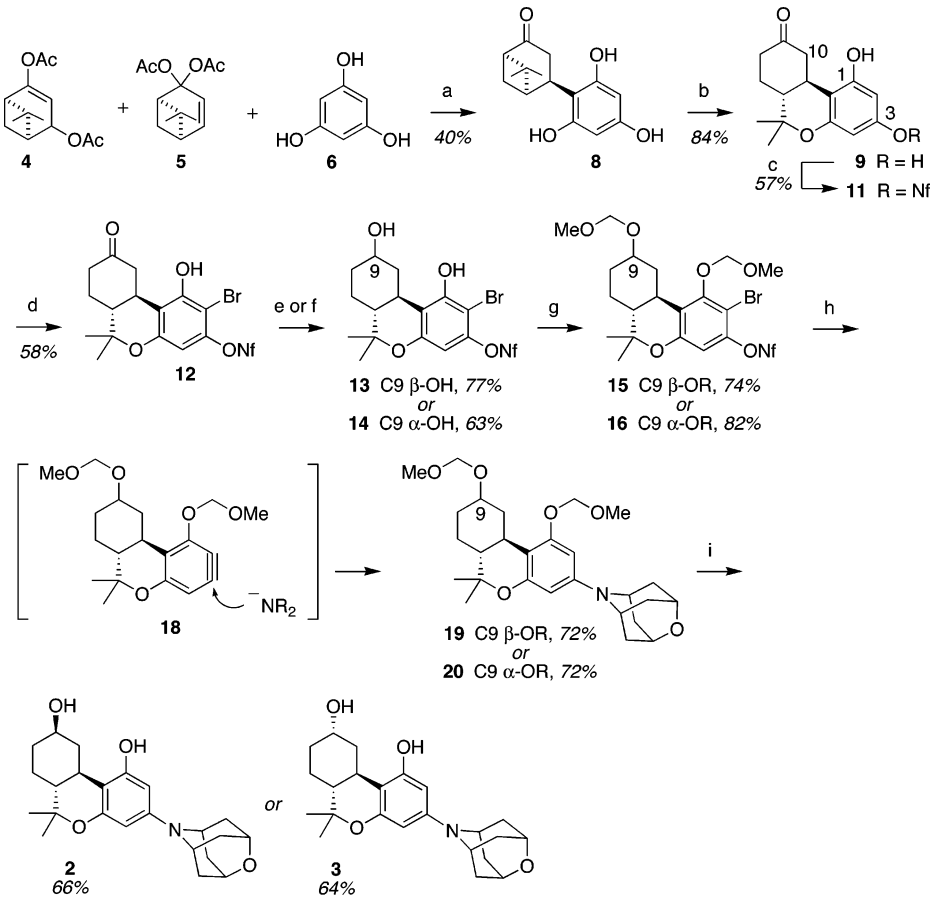
(14) Drake, D. J.; Jensen, R. S.; Busch-Petersen, J.; Kawakami, J. K.; Conception Fernandez-Garcia, M.; Fan, P.; Makriyannis, A.; Tius, M. A. *J. Med. Chem.* **1998**, *41*, 3596−3608.

(15) Zhang, X.; Sui, Z. *Tetrahedron Lett.* **2003**, *44*, 3071−3073.

(16) Neuville, L.; Bigot, A.; Tran Huu Dau, M. E.; Zhu, J. *J. Org. Chem.* **1999**, *64*, 7638−7642.

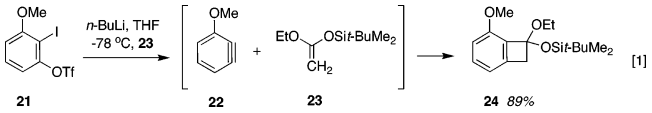
(17) Buchwald has reported palladium-catalyzed aminations of aryl nonaflates: Anderson, K. W.; Mendez-Perez, M.; Priego, J.; Buchwald, S. *J. Org. Chem.* **2003**, *68*, 9563−9573.

SCHEME 1[a]



[a] (a) *p*-TsOH, CH_2Cl_2/acetone (4/1), rt, 20 min; 40%. (b) $SnCl_4$, $MeNO_2$, rt, 20 h; 84%. (c) CsF, **10**, DMF, rt, 12 h; 57%. (d) 2,4,4,6-Tetrabromocyclohexadienone, $CHCl_3$/*p*-dioxane 0 °C to room temperature, overnight; 58%. (e) $NaBH_4$, THF/*i*-PrOH, rt, 40 min; 77% **13** + trace **14**. (f) K-Selectride, THF, −78 °C to room temperature, 3 h; 63%. (g) $MeOCH_2Cl$, $(i\text{-Pr})_2NEt$, CH_2Cl_2, 0 °C to room temperature, 5 h; **15**, 74%; **16**, 82%. (h) **17**, *n*-BuLi, THF, −78 °C, 20 min; **19**, 72%; **20**, 72%. (i) TMSBr, CH_2Cl_2, −40 °C, 3 h; **2**, 66%; **3**, 64%.

the polarization of the triple bond and suggests that for electronic, as well as steric, reasons the addition of **17** (as its conjugate base) to benzyne **18** (Scheme 1) will lead to the desired C3-substituted cannabinoid.[19]



Tricyclic nonaflate **11** (Scheme 1) was brominated according to the conditions described by Trost and Toste to produce bromide **12** in 58% yield.[20] The conditions for this reaction must be chosen carefully so as to avoid introducing multiple bromine atoms into the highly activated aromatic. Because it was our goal to produce both diastereomers of the C9 alcohol, the carbonyl group in **12** was first reduced with $NaBH_4$ to give C9 β (equatorial) alcohol **13** in 77% yield, accompanied by a trace of the C9 α (axial) diastereomer **14**. Alcohol **14** was the exclusive product when **12** was reduced with K-Selectride at −78 °C. The two diastereomers were readily distinguishable on the basis of the C9 carbinol proton NMR chemical shift and multiplicity. In **13**, the C9 proton appears as a multiplet at 3.79−3.88 ppm ($CDCl_3$, 300 MHz), which is consistent with an axial proton. In **14**, the proton at C9 appears as a broad singlet at 4.28 ppm, as is consistent for an equatorial proton.

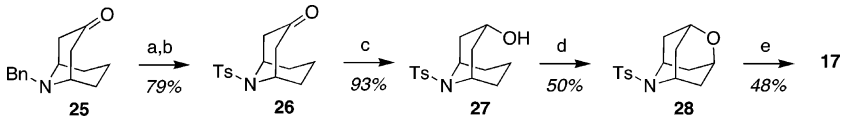
Both hydroxyl groups in **13** and **14** were protected simultaneously as the methoxymethyl ether derivatives, leading to **15** (74% yield) and **16** (82% yield), respectively. The key reaction, benzyne generation, followed by addition of the conjugate base of **17**, was carried out by treating a solution of **15** and 2.4 equiv of **17** in THF with 4.8 equiv of *n*-BuLi at −78 °C. The reaction was rapid and clean and led to **19** in 72% yield. The process was repeated with **16**, leading to **20** in 72% yield as well. It is noteworthy that if any addition of *n*-BuLi to the benzyne takes place it represents a minor side reaction. The deprotonation of **17** to produce the amide must be faster than lithium−bromine exchange because no quenching of benzyne by proton transfer was observed. An excess of **17** was used in these reactions; however, the unreacted amine was recovered and reused. The benzynes that are generated from **15** and **16** represent versatile reactive intermediates that should be suitable for the synthesis of diverse tricyclic cannabinoids.

(18) (a) Hamura, T.; Hosoya, T.; Yamaguchi, H.; Kuriyama, Y.; Tanabe, M.; Miyamoto, M.; Yasui, Y.; Matsumoto, T.; Suzuki, K. *Helv. Chim. Acta* **2002**, *85*, 3589−3604. (b) Hamura, T.; Ibusuki, Y.; Uekusa, H.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **2006**, *128*, 3534−3535. (c) Hosoya, T.; Hasegawa, T.; Kuriyama, Y.; Matsumoto, T.; Suzuki, K. *Synlett* **1995**, *2*, 177−179. For related work, see: Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198−3209.

(19) Hosoya, T.; Hasegawa, T.; Kuriyama, Y.; Suzuki, K. *Tetrahedron Lett.* **1995**, *36*, 3377−3380.

(20) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 3090−3100.

SCHEME 2[a]



[a] (a) Pd/C, HOAc, H_2, rt, 3 days; HCl, H_2O. (b) TsCl, Na_2CO_3, H_2O/CH_2Cl_2 (1/1), rt, 12 h; 79% from **25**. (c) $LiAlH_4$, Et_2O, rt, 4 h; 93%. (d) $PhI(OAc)_2$, I_2, hν, C_6H_{12}, 50 °C, 1 h; 50% + ca. 20% of **26**. (e) Na, naphthalene, DME, −50 °C, 10 min; 48%.

The last step of the synthesis, removal of the two methoxymethyl protecting groups from **19** and **20**, proved to be unexpectedly difficult. For example, exposure of either **19** or **20** to conventional deprotection protocols (HCl, PPTS) led to aminodiol products in less than 50% yield in slow reactions. The reason for this is not obvious but may be related to the buffering effect of the nitrogen atom. Protecting group removal was accomplished successfully according to Hanessian's procedure,[21] by treating **19** and **20** with TMSBr in dichloromethane at −40 °C for 3 h. The yields of **2** and **3** were 66% and 64%, respectively.

The synthesis of oxaza adamantane **17** deserves some comment. A synthesis of **17** has been described by Stetter[10] and co-workers in six steps from 1,5-cyclooctadiene, in which the oxa bridge was installed through a bis bromoetherification process. A similar synthesis of **17** has been described by Portmann, in which the oxa bridge was introduced through a bis oxymercuration process.[11] Because both syntheses commence with 1,5-cyclooctadiene and lead to mixtures of bicyclo [3.3.1] and bicyclo [4.2.1] isomers, we were motivated to develop the synthesis of **17** that is summarized in Scheme 2.

Aminoketone **25** has been prepared by Momose and co-workers in a single step in 78% yield from benzylamine hydrochloride, acetone dicarboxylic acid, and glutaraldehyde.[22] Hydrogenolytic cleavage of the benzyl protecting group, followed by N-tosylation, led to tosylate **26** in 79% yield. Ketone reduction gave alcohol **27** in 93% yield. Oxidative closure of the pyran ring was accomplished photochemically in the presence of $PhI(OAc)_2$ and iodine according to Marchand and co-workers' procedure in 50% yield.[23] The *N*-benzyl protecting group was not compatible with the conditions for the oxidative cyclization, hence the need for the *N*-tosylate. Reductive cleavage of the tosylate led to **17**.[24]

Conclusions

In conclusion, synthesis of the first heteroadamantyl cannabinoids has been described. The key step is the condensation of the oxaza adamantane with a benzyne that is derived from the tricyclic cannabinoid nucleus. This represents a new strategy for the regiospecific introduction of substituents at C3 that will be generally useful for cannabinoid synthesis.[25,26] It is significant that regiospecificity is likely to be observed *regardless* of the steric requirement of the substituent because of the electronic bias for C3 attack on the benzyne referred to above. In this context, it is worth noting that steric steering by the *tert*-alkyl substituent in resorcinol **7** determines the regiospecificity during acid-catalyzed condensation with acetates **4** and **5**. Absent the *tert*-alkyl group on the aromatic fragment, this approach cannot be applied because mixtures of regioisomeric condensation products are invariably formed. In the approach that has been described above, the symmetry of the phloroglucinol renders the issue moot during the condensation with **4** and **5**. This allows us to retain the attractive features of the Lilly synthesis of nabilone without the requirement for a sterically bulky substituent on the aromatic ring. This method is currently being applied to the synthesis of a series of heteroadamantyl cannabinoids related to **2** and **3**. The syntheses of these materials and their binding affinities to CB1 and CB2 for the series will be reported in future publications.

Experimental Section

(1*R*,4*R*,5*R*)-6,6-Dimethyl-4-(2,4,6-trihydroxyphenyl)bicyclo-[3.1.1]heptan-2-one 8. To a solution of phloroglucinol (500 mg, 3.97 mmol) and diacetates **4** and **5** (1.15 g, 4.76 mmol) in CH_2Cl_2/acetone (4/1) at 0 °C was added TsOH (820 mg, 4.76 mmol). The resulting mixture was stirred at room temperature for 20 min and then quenched with aqueous $NaHCO_3$ solution. The organic phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated to dryness. Purification of the crude reaction mixture by flash column chromatography on silica gel (eluent: EtOAc/Hexane 3/7) afforded product **8** (416 mg, 40% yield) as a white powder: mp 110−120 °C; R_f = 0.29 (60% EtOAc in hexanes); $[\alpha]^{25}_D$ +54.3 (*c* 3.55, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 0.94 (s, 3H), 1.35 (s, 3H), 2.14 (t, J = 6.0 Hz, 1H), 2.35−2.48 (m, 3H), 2.57−2.62 (m, 1H), 3.67 (dd, J = 7.5, 18.6 Hz, 1H), 3.95 (t, J = 8.1 Hz, 1H), 5.85 (s, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 22.4, 24.9, 26.6, 30.0, 38.8, 43.2, 48.8, 59.3, 95.9, 108.9, 157.3, 158.5, 220.2; IR (neat) 2929, 1655, 1612, 1467, 1373, 1265, 1156, 1014 cm^{-1}; mass spectrum (EI) *m*/*z* 262 (56), 219 (32), 179 (57), 177 (37), 165 (85), 152 (100), 139 (79), 126 (88), 93 (40), 83 (100), 77 (36), 69 (63); exact mass calculated for $C_{15}H_{18}O_4$ 262.1200, found 262.1231.

(6a*R*,10a*R*)-1,3-Dihydroxy-6,6-dimethyl-7,8,10,10a-tetrahydro-6*H*-benzo[*c*]chromen-9(6a*H*)-one 9. To a solution of **8** (100 mg, 0.38 mmol) in nitromethane (10 mL) was added $SnCl_4$ (375 μL, 3.2 mmol). The resulting mixture was stirred at room temperature for 20 h and then poured onto ice and extracted with Et_2O. The organic extracts were combined, washed with 1 M HCl solution, water, and aqueous $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated to dryness. Purification of the crude reaction mixture by flash column chromatography on silica gel (eluent: EtOAc/Hexane 3/7) afforded product **9** (84 mg, 84% yield) as a white powder: mp 140−150 °C; R_f = 0.32 (50% EtOAc in hexanes); $[\alpha]^{25}_D$ −64.6 (*c* 0.85, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 1.08 (s, 3H), 1.42

(21) Hanessian, S.; Delorme, D.; Dufresne, Y. *Tetrahedron Lett.* **1984**, *25*, 2515−2518. For an example of the application of this method to a polyfunctional molecule, see: Judd, T. C.; Williams, R. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4683−4685.

(22) Momose, T.; Toshima, M.; Toyooka, N.; Hirai, Y.; Eugster, C. H. *J. Chem. Soc., Perkin Trans. 1* **1997**, *9*, 1307−1313.

(23) Marchand, A. P.; Kumar, V. S.; Hariprakasha, H. K. *J. Org. Chem.* **2001**, *66*, 2072−2077.

(24) In recent work, we have determined that the yield of the reductive cleavage step can be improved greatly by limiting the amount of water that is used during workup, thereby minimizing losses of product.

(25) For a review of cannabinoid synthesis, see: Tius, M. A. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1997; Vol. 19, p 185.

(26) For an alternative approach to the synthesis of C3 amino cannabinoids, see: Petrzilka, T.; Lusuardi, W. G. *Helv. Chim. Acta* **1973**, *56*, 510−518.

(s, 3H), 1.45−1.57 (m, 1H), 1.92 (td, J = 2.4, 12.3 Hz, 1H), 2.02−2.18 (m, 2H), 2.47−2.25 (m, 2H), 2.69−2.78 (m, 1H), 3.78−3.84 (m, 1H), 5.76 (d, J = 2.4 Hz, 1H), 5.85 (d, J = 2.4 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 19.0, 27.9, 28.1, 36.0, 41.5, 46.8, 77.8, 96.6, 96.7, 104.3, 111.2, 156.6, 158.3, 214.6; IR (neat) 2973, 1690, 1620, 1462, 1366, 1134, 1015 cm^{-1}; mass spectrum (EI) m/z 262 (100), 247 (29), 205 (21), 179 (57), 152 (85), 139 (26), 126 (12), 93 (40), 77 (11), 69 (39); exact mass calculated for $C_{15}H_{18}O_4$ 262.1200, found 262.1185.

Benzyne Generation and Trapping. Preparation of 19. To a solution of bromononaflate **15** (190 mg, 0.27 mmol) and oxaza adamantane **17** (90 mg, 0.65 mmol) in 1 mL of THF at −78 °C was added dropwise *n*-BuLi (550 μL, 1.3 mmol, solution in hexane). The mixture was stirred for 20 min, quenched with H_2O, and extracted with Et_2O (3×). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated to dryness. Purification of the crude reaction mixture by flash column chromatography on silica gel (eluent: EtOAc/hexane 3/7) afforded product **19** (89 mg, 72% yield) as an oil: R_f = 0.23 (30% EtOAc in hexanes); $[\alpha]^{25}_D$ −23.7 (*c* 0.56, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD) δ 0.94 (s, 3H), 1.05−1.20 (m, 2H), 1.25 (s, 3H), 1.28−1.38 (m, 1H), 1.80−1.85 (dm, 4H), 1.90−1.95 (dm, 4H), 2.06 (dm, 1H), 2.28−2.36 (td, J = 2.7, 11.4 Hz, 1H), 3.27 (s, 3H), 3.29−3.35 (m, 1H), 3.38 (s, 3H), 3.57 (m, 1H), 3.96 (s br, 2H), 4.05 (s br, 2H), 4.62 (s, 2H), 5.02 (d, J = 6.6 Hz, 1H), 5.07 (d, J = 6.9 Hz, 1H), 5.92 (d, J = 2.4 Hz, 1H), 6.18 (d, J = 2.7 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 19.1, 27.2, 28.2, 34.2, 34.3, 34.4, 34.9, 38.5, 50.4, 55.5, 56.6, 68.8, 77.4, 77.8, 95.9, 96.0, 96.3, 98.9, 106.1, 150.7, 156.8, 159.0; IR (neat) 2939, 1615, 1564, 1496, 1151, 1107, 1054, 1026 cm^{-1}; mass spectrum (EI) m/z 473 (M^+, 100), 412 ($M^+ - OCH_2CH_3$, 9), 205 (6), 152 (28); exact mass calculated for $C_{27}H_{39}NO_6$ 473.2800, found 473.2776.

Benzyne Generation and Trapping. Preparation of 20. To a solution of bromononaflate **15** (126 mg, 0.18 mmol) and oxaza adamantane **17** (61 mg, 0.44 mmol) in 1 mL of THF at −78 °C was added dropwise *n*-BuLi (370 μL, 0.9 mmol, solution in hexane). The mixture was stirred for 20 min, quenched with H_2O, and extracted with Et_2O (3×). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated to dryness. Purification of the crude reaction mixture by flash column chromatography on silica gel (eluent: EtOAc/hexane 3/7) afforded product **20** (60 mg, 72% yield) as a solid: mp 104−106 °C; R_f = 0.26 (30% EtOAc in hexanes); $[\alpha]^{25}_D$ −65.4 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD) δ 1.06 (s, 3H), 1.09−1.18 (m, 1H), 1.34 (s, 3H), 1.40−1.70 (m, 5H), 1.90−2.04 (m, 8H), 2.78−2.84 (m, 1H), 3.29−3.35 (m, 1H), 3.42 (s, 3H), 3.47 (s, 3H), 3.98 (m, 1H), 4.05 (s br, 2H), 4.15 (s br, 2H), 4.70 (d, J = 6.9 Hz, 1H), 4.81 (d, J = 6.9 Hz, 1H), 5.11−5.17 (m, 2H), 6.01 (d, J = 2.4 Hz, 1H), 6.27 (d, J = 2.4 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 19.3, 24.3, 28.0, 30.6, 32.5, 34.2, 34.3, 35.9, 50.8, 55.6, 56.5, 68.8, 72.7, 77.8, 95.4, 95.9, 96.3, 98.9, 106.7, 150.5, 157.0, 159.0; IR (neat) 2939, 1616, 1563, 1497, 1148, 1109, 1039 cm^{-1}; mass spectrum (EI) m/z 473 (M^+, 100), 412 ($M^+ - OCH_2CH_3$, 17), 367 (24), 298 (5); exact mass calculated for $C_{27}H_{39}NO_6$ 473.2800, found 473.2752.

Tricyclic Cannabinoid 2. To a solution of compound **19** (71 mg, 0.15 mmol) in 1 mL of CH_2Cl_2 at −40 °C was added dropwise TMSBr (2.25 mL, 0.9 mmol) in solution in CH_2Cl_2 in 6 aliquots over 3 h. The mixture was stirred for 1 h at −40 °C, quenched with H_2O, and extracted with CH_2Cl_2 (3×). The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness. Purification of the crude reaction mixture by flash column chromatography on silica gel (eluent: EtOAc/hexane 8/2) afforded product **2** (38 mg, 66% yield) as an oil: R_f = 0.14 (30% EtOAc in hexanes); $[\alpha]^{25}_D$ −84.2 (*c* 0.90, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 0.93 (q, J = 11.7 Hz, 1H), 1.04 (s, 3H), 1.14−1.44 (m, 6H), 1.85−2.12 (m, 10H), 2.38 (td, J = 2.7, 11.1 Hz, 1H), 3.44−3.50 (m, 1H), 3.68−3.77 (m, 1H), 4.02 (s br, 2H), 4.14 (s br, 2H), 5.87 (d, J = 2.4 Hz, 1H), 5.97 (d, J = 2.4 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 19.2, 27.2, 28.3, 34.2, 34.7, 36.7, 40.4, 49.1, 50.4, 68.8, 71.4, 77.8, 96.5, 96.8, 104.3, 150.4, 157.1, 158.6; IR (neat) 2935, 1621, 1569, 1515, 1440, 1333, 1189, 1139, 1053 cm^{-1}; mass spectrum (EI) m/z 385 (M+, 100), 367 ($M^+ - H_2O$, 42), 348 (152), 326 (17), 298 (23), 260 (6); exact mass calculated for $C_{23}H_{31}NO_4$ 385.2300, found 385.2225.

Tricyclic Cannabinoid 3. To a solution of compound **20** (32.6 mg, 0.07 mmol) in 1 mL of CH_2Cl_2 at −40 °C was added dropwise TMSBr (1.05 mL, 0.42 mmol) in solution in CH_2Cl_2 in 6 aliquots over 3 h. The mixture was stirred for 1 h at −40 °C, quenched with H_2O, and extracted with CH_2Cl_2 (3×). The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness. Purification of the crude reaction mixture by flash column chromatography on silica gel (eluent: EtOAc/hexane 8/2) afforded product **3** (17 mg, 64% yield) as an oil: R_f = 0.20 (30% EtOAc in hexanes); $[\alpha]^{25}_D$ −42.3 (*c* 0.93, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 1.08 (s, 3H), 1.13−1.22 (m, 1H), 1.29−1.66 (m, 9H), 1.90−2.03 (m, 8H), 2.87 (td, J = 2.7, 11.4 Hz, 1H), 3.30−3.37 (m, 1H), 4.02 (s br, 2H), 4.14 (s br, 2H), 5.87 (m, 1H), 5.96 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 19.4, 23.6, 28.1, 30.9, 34.2, 38.0, 51.0, 67.6, 68.8, 77.7, 96.6, 96.9, 104.9, 150.2, 157.2, 158.6; IR (neat) 2938, 1621, 1568, 1514, 1440, 1334, 1189, 1138, 1064 cm^{-1}; mass spectrum (EI) m/z 385 (M^+, 100), 367 ($M^+ - H_2O$, 72), 348 (22), 298 (38), 247 (6), 205 (19); exact mass calculated for $C_{23}H_{31}NO_4$ 385.2300, found 385.2248.

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Supporting Information Available: Spectroscopic data (^{1}H and ^{13}C NMR) for **2**, **3**, **8**, **9**, **11**−**16**, **19**, **20**, **27**, and **28**. Experimental conditions for the synthesis of **11**−**17** and **26**−**28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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