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Synthesis and characterization of a compact tricyclic resorcinol from (+)- and (–)-3-pinanol

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Abstract

Resorcinol derivatives are important building blocks in the synthesis of natural products and pharmaceutical compounds including cannabinoids. Here we describe the synthesis and the structural characterization of a key resorcinol which carries a fully restricted bridged bicyclic group. We also report a potential mechanism for the acid catalyzed condensation of (+)- or (–)-3-pinanol with 2,6-dimethoxyphenol. The synthesized resorcinol facilitates the development of novel conformationally restricted cannabinoid analogs.

Keywords

3-pinanol; resorcinol; cannabinoids

Introduction

A review of structure activity relationship (SAR) studies recognizes two pharmacophores within the classical (–)-⁸-tetrahydrocannabinol prototype ((–)-⁸-THC, **1**, Figure 1): a phenolic hydroxyl at C1, and a lipophilic side chain at C3.^{1,2} Of these, the side chain plays a crucial role in determining the compound's affinity and pharmacological potency for cannabinoid receptors (CBs).^{1–4} In the course of our program aimed at developing potent and selective cannabinoids we have focused on analogs with conformationally restricted and bulky side chains.^{5–14} In this regard, the aliphatic C3 side chain was substituted with C1' cyclic groups,^{5–8} or partially immobilized by a fused six membered ring,^{10,15} or replaced by the bulky adamantyl, heteroadamantyl, bornyl and isobornyl substituents.^{11–14} Some of these analogs showed enhanced CB receptor subtype selectivity and affinity as well as remarkable *in vivo* potency. They have also served as valuable biochemical and pharmacological tools towards understanding the cannabinoid ligand-receptor interactions.

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Supplementary Data

Experimental procedures and spectroscopic and physical data for all compounds. Supplementary data associated with this article can be found, in the online version, at Science Direct.

However, cannabinoid analogs with fully restricted side chains have not been developed so far. Here we describe our work for the synthesis and characterization of a key tricyclic resorcinol which facilitates the development of novel rigid and compact cannabinoid analogs.

3-Pinanol (Figure 1) was selected as the source of the fully restricted side chain pharmacophore for two reasons: 1) it represents a ten carbon compact isostere of the successful cannabimimetic adamantyl, heteroadamantyl, bornyl and isobornyl groups,^{9,11–14} and 2) it could form putative reactive intermediates (**11** or **12**, Figure 2) with two reactive centers (i.e., the carbocationic carbon and the double bond), which provides a unique opportunity for constructing a fully restricted cannabinoid side chain, in a single step, through a sequence of Friedel-Crafts alkylation reactions.

Results and Discussion

Synthesis of the racemic resorcinol **4** with the fully restricted side chain is summarized in Scheme 1. Following reaction conditions we described for the preparation of 1-adamantyl resorcinol,¹² 2,6-dimethoxyphenol (**5**) and (+)-3-pinanol (**2**, 95% ee) were exposed in 70% methanesulfonic acid and heated at 70°C for 12 hours. The reaction provided a racemic mixture ($[\alpha]_D^{26} = 0$, $c = 1$, EtOH) as the major product (53% yield, 78% based on recovered **5**) whose 1D and 2D NMR spectra supported the structure of **6a** and **6b**. Conventionally, only the enantiomer **6b** is shown in Scheme 1. Unreacted 2,6-dimethoxyphenol (34%) was recovered during the purification of the crude reaction mixture while minor byproducts were not isolated and characterized. Recrystallization of racemic **6** from dichloromethane/hexane (1:1) afforded crystals suitable for x-ray analysis (Figure 4), thus providing direct evidence on the structure of 3,5-dimethoxy-8,8,12-trimethyl-tricyclo-[7.3.1.0^{2,7}]-trideca-2,4,6-trien-4-ol (**6**). When (+)-3-pinanol (**2**) was replaced with (–)-3-pinanol (**3**, 95% ee) the same racemic compound was produced. This confirms that the reaction proceeds in a non-stereospecific manner.

The formation of a relatively complex product from simple starting materials, in a single step, deserves some discussion. It is anticipated that the tertiary *p*-menth-1-en-8-yl carbocation **11** (Figure 2) is a reactive intermediate in the synthesis of racemic resorcinol **6**. It should be noted that generation of such a species in acidic environment is also supported by the following observations: 1) intermediate **12** has been trapped with aliphatic nitriles in a Ritter reaction employing (–)-3-pinanol in the presence of sulfuric acid,¹⁷ and 2) carbocations **11** and **12** are the reactive intermediates that lead to α -terpineol during the acid catalyzed hydration of α -pinene in a laboratory as well as industrial scale.^{18–23} Most likely, (+)-3-pinanol (**2**) in the presence of acid catalyst affords the secondary carbocation **9** which undergoes 1,2-hydride shift to give the more stable tertiary carbocation **10**. Rearrangement of **10** to **11** takes place as a result of relief from the strain imposed by the cyclobutane ring. Analogously, (–)-3-pinanol (**3**) can lead to the respective carbocation **12**.

The carbocationic carbon and the double bond in **11** and **12** are both reactive centers¹⁷ available for a sequence of Friedel-Crafts alkylation reactions (Figure 3). Thus, terpenylation of 2,6-dimethoxyphenol (**5**) with **11** or **12** leads to **13** and **14** respectively as a result of the *para*-directing effect of the phenolic hydroxyl group. For the formation of the intramolecular Friedel-Crafts product **6b**, the cyclohexene ring of **13** might adopt a "folded" active conformation that brings the aromatic ring to the close proximity of the cyclohexene ring. In the presence of acid, this conformational change enables formation of a bridged carbocation **15** where the methyl group is in *trans* orientation with respect to the large gem-dimethyl-aryl substituent. The process ends with the formation of the thermodynamically

avored six membered ring as in the related Bogert-Cook synthesis of phenanthrene.^{24,25} Similarly, enantiomer **6a** could be produced from either **13** or **14**.

Exposure of **6** to diethylphosphonate afforded phosphonate ester **7** (97% yield, Scheme 1) which upon treatment with Li/NH₃ at -78°C gave the resorcinol dimethyl ether **8** (92% yield). This was followed by demethylation employing boron tribromide to give the final product **4** in excellent yield (92%).

In summary, we describe here the synthesis and the structural characterization of a resorcinol with a fully restricted bridged bicyclic group. We also report a probable mechanism for the condensation of (+)- or (-)-3-pinanol with 2,6-dimethoxyphenol, which results in the formation of a relatively complex product from simple starting materials in a single step. The key resorcinol (compound **4**) identified in this study is currently being elaborated into the synthesis of novel cannabinoid analogs with fully restricted side chain. Preliminary biological testing found them active at cannabinoid receptors. A detailed SAR study along with a full biological evaluation of the cannabinoid analogs structurally related to resorcinol **4** is currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References and Notes

1. Thakur GA, Nikas SP, Li C, Makriyannis A. *Handb. Exp. Pharmacol.* 2005;209. [PubMed: 16596776]
2. Thakur GA, Nikas SP, Makriyannis A. *Mini Rev. Med. Chem.* 2005; 5:631. [PubMed: 16026309]
3. Lu D, Vemuri VK, Duclos RI Jr, Makriyannis A. *Curr. Top. Med. Chem.* 2006; 6:1401. [PubMed: 16918457]
4. Pavlopoulos S, Thakur GA, Nikas SP, Makriyannis A. *Curr. Pharm. Des.* 2006; 12:1751. [PubMed: 16712486]
5. Nikas SP, Alapafuja SO, Papanastasiou I, Paronis CA, Shukla VG, Papahatjis DP, Bowman AL, Halikhedkar A, Han X, Makriyannis A. *J. Med. Chem.* 2010; 53:6996. [PubMed: 20925434]
6. Papahatjis DP, Nahmias VR, Nikas SP, Andreou T, Alapafuja SO, Tsotinis A, Guo J, Fan P, Makriyannis A. *J. Med. Chem.* 2007; 50:4048. [PubMed: 17672444]
7. Papahatjis DP, Nikas SP, Andreou T, Makriyannis A. *Bioorg. Med. Chem. Lett.* 2002; 12:3583. [PubMed: 12443781]
8. Papahatjis DP, Nikas SP, Kourouli T, Chari R, Xu W, Pertwee RG, Makriyannis A. *J. Med. Chem.* 2003; 46:3221. [PubMed: 12852753]
9. Duclos RI, Lu D, Guo JX, Makriyannis A. *Tetrahedron Lett.* 2008; 49:5587. [PubMed: 23935221]
10. Khanolkar AD, Lu D, Fan P, Tian X, Makriyannis A. *Bioorg. Med. Chem. Lett.* 1999; 9:2119. [PubMed: 10465529]
11. Lu D, Guo J, Duclos RI Jr, Bowman AL, Makriyannis A. *J. Med. Chem.* 2008; 51:6393. [PubMed: 18826296]
12. Lu D, Meng Z, Thakur GA, Fan P, Steed J, Tartal CL, Hurst DP, Reggio PH, Deschamps JR, Parrish DA, George C, Jarbe TU, Lamb RJ, Makriyannis A. *J. Med. Chem.* 2005; 48:4576. [PubMed: 15999995]
13. Dixon DD, Sethumadhavan D, Benneche T, Banaag AR, Tius MA, Thakur GA, Bowman A, Wood JT, Makriyannis A. *J. Med. Chem.* 2010; 53:5656. [PubMed: 20593789]

14. Le Goanvic D, Tius MA. J. Org. Chem. 2006; 71:7800. [PubMed: 16995689]
15. Huffman JW, Yu S. Bioorg. Med. Chem. 1998; 6:2281. [PubMed: 9925290]
17. Kovalskaya SS, Kozlov NG, Kalechits GV. J. Org. Chem. USSR (English Trans.). 1991; 27:649.
18. Avila MC, Comelli NA, Rodriguez-Castellon E, Jimenez-Lopez A, Flores RC, Ponzi EN, Ponzi MI. J. Mol. Catal. a-Chem. 2010; 322:106.
19. Liu SW, Yu ST, Liu FS, Xie CX, Li L, Ji KH. J. Mol. Catal. a-Chem. 2008; 279:177.
20. Radbil' AB, Zolin BA, Shkapova YA, Radbil' BA. Russ. J. Appl. Chem. 2002; 75:310.
21. Roman-Aguirre M, De la Torre-Saenz L, Flores WA, Robau-Sanchez A, Elgueabal AA. Catal. Today. 2005; 107-08:310.
22. Vital J, Ramos AM, Silva IF, Valente H, Castanheiro JE. Catal. Today. 2000; 56:167.
23. Yadav MK, Patil MV, Jasra RV. J. Mol. Catal. a-Chem. 2009; 297:101.
24. Bogert MT. Science. 1933; 77:289. [PubMed: 17780265]
25. Cook JW, Hewett CL. J. Chem. Soc. 1933:1098.

Figure 1.
Structures of (-)- Δ^8 -tetrahydrocannabinol, 3-pinanol and tricyclic resorcinol.

Figure 2.
Generation of carbocations **11** and **12**.

Figure 3.
Probable mechanism for the preparation of **6b**.

Figure 4.
ORTEP structure of 6.

Scheme 1.

Synthesis of resorcinol **4**. Reagents and conditions: (a) (+)- or (-)-3-pinanol, 70% $\text{CH}_3\text{SO}_3\text{H}$, 70°C, 12 h, 53% (78% based on recovered starting material); (b) HP(O)(OEt)_2 , Et_3N , CCl_4 , 0°C to r t, overnight, 97%; (c) Li/NH_3 , -78°C, 1 h, 92%; (d) BBr_3 , CH_2Cl_2 , 0°C to r t, 12 h, 92%.