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Synthesis of *Para* (−)-Δ^8-THC Triflate as a Building Block for the Preparation of THC Derivatives Bearing Different Side Chains

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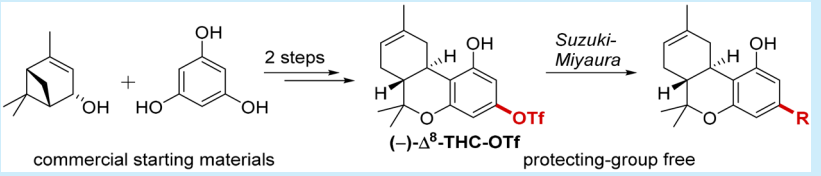
Supporting Information



ABSTRACT: A two-step synthesis of *para* (−)-Δ^8-THC-OTf that can be used as building block for late-stage introduction of side chains to the tetrahydrodibenzopyran core of THC by cross-coupling chemistry is presented. No protecting groups are needed, and (−)-Δ^8-THC-OTf can be cross-coupled to access derivatives bearing pharmacologically interesting side chains such as benzoyl units, sterically demanding groups, aromatic chains, and alkenyl groups. This approach allowed an efficient four-step synthesis of (−)-Δ^8-THC from commercial materials.

Cannabis sativa L. contains more than 70 cannabinoids[1] of which the main psychoactive compound (−)-Δ^9-THC was identified in 1964 by Gaoni and Mechoulam,[2] and more than 20 years later the cannabinoid receptors CB_1 and CB_2 were discovered.[3] Since CBs are involved in many different physiological processes,[4] understanding the structure−activity relationship of THC plays an important role in drug development. Under acidic conditions, (−)-Δ^9-THC isomerizes to its thermodynamically more stable double bond isomer (−)-Δ^8-THC (Figure 1). Although the Δ^8 isomer is less

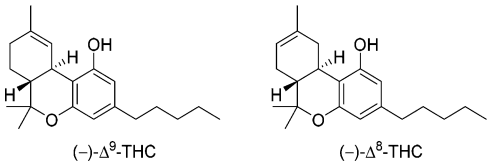


Figure 1. Structures of natural products (−)-Δ^9-THC and (−)-Δ^8-THC.

abundant in natural cannabis, both isomers are almost equipotent in terms of cannabinoid receptor interaction.[5] The structure of THC comprises a tetrahydrodibenzopyran core connected to a pentyl side chain. In medicinal chemistry, the influence of structural modifications of THC on the affinity, selectivity, and potencies for the cannabinoid receptors has been investigated. In the course of this, various studies have focused on substituting the pentyl side chain since this alkyl group has been recognized as a critical pharmocophoric moiety.[5−7]

Various elegant syntheses towards (−)-Δ^9-THC and (−)-Δ^8-THC have been published;[8] some of them are based on the acid-catalyzed condensation of resorcinols with natural terpenoids.[9] In the first published THC synthesis, Mechoulam, Braun, and Gaoni synthesized THC by an acid-catalyzed Friedel−Crafts alkylation and subsequent O-cyclization of (*S*)-*cis*-verbenol and olivetol (Scheme 1, A).[9d] The cascade likely proceeds via regioselective Friedel−Crafts alkylation to give intermediate **A**. Protonation of **A** and subsequent cleavage of the strained four-membered ring in **B** leads to the tertiary cation **C**, which finally cyclizes via C−O bond formation with the phenolic OH group to give (−)-Δ^8-THC.

We successfully used the same strategy in our previous work to construct the hexahydrodibenzopyran core of (−)-machaeriols B and D from verbenol and a resorcinol derivative (Scheme 1, B).[10] In both cases, Friedel−Crafts alkylation takes place at the carbon atom between the two phenolic OH groups of the resorcinol, probably steered by the bulky pentyl and benzofuryl substituents. Applying the same strategy, we attempted to synthesize a bromo-substituted THC that can be later used as a building block for late-stage diversification applying cross-coupling chemistry. This strategy should offer the possibility of readily accessing various THC analogues from a single starting compound. Along these lines, Trauner and Carreira recently presented a six-step synthesis of (−)-Δ^9-Br-THC that was used for further diversification by attaching different side chains using cross-coupling chemistry.[11]

Unexpectedly, the reaction of verbenol with bromoresorcinol did not give the targeted *para* Br-THC. We isolated the other regioisomer, with the bromo substituent positioned *ortho* to the pyran ring (Scheme 1, B). Unfortunately, in our initial paper[10] the structure, based on a literature report[9a] was not correctly assigned. Such *ortho* THC regioisomers have occasionally been mentioned as side products in reactions of resorcinols with terpene derivatives, especially when rather

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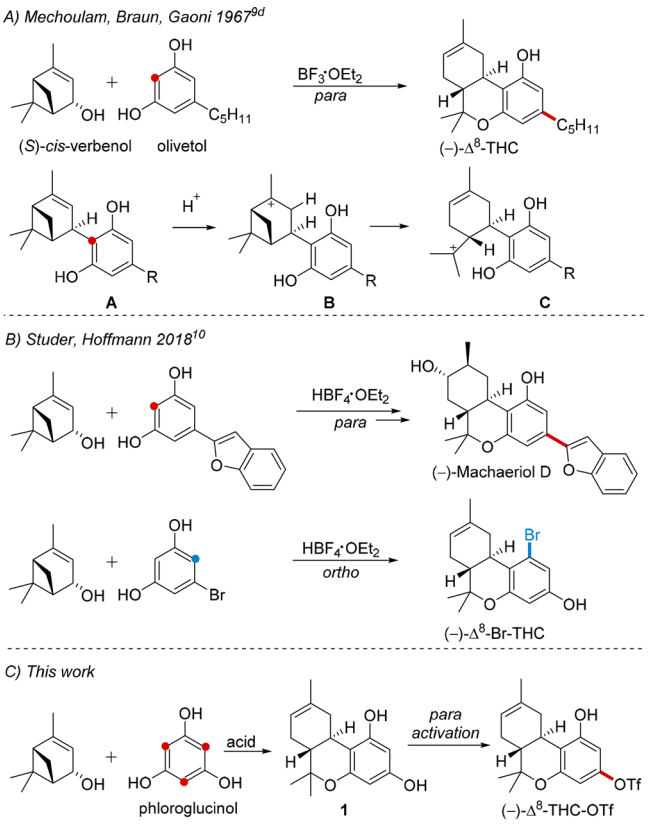
Scheme 1. (A) Friedel–Crafts Alkylation and Subsequent Cyclization of (*S*)-*cis*-Verbenol and Olivetol to (−)-Δ⁸-THC.[9d] (B) Previous Synthesis of Machaeriols and (−)-Δ⁸-Br-THC.[10] (C) Novel Approach to *Para* (−)-Δ⁸-THC Triflate as a General Building Block for Late-Stage Diversification by Cross-Coupling

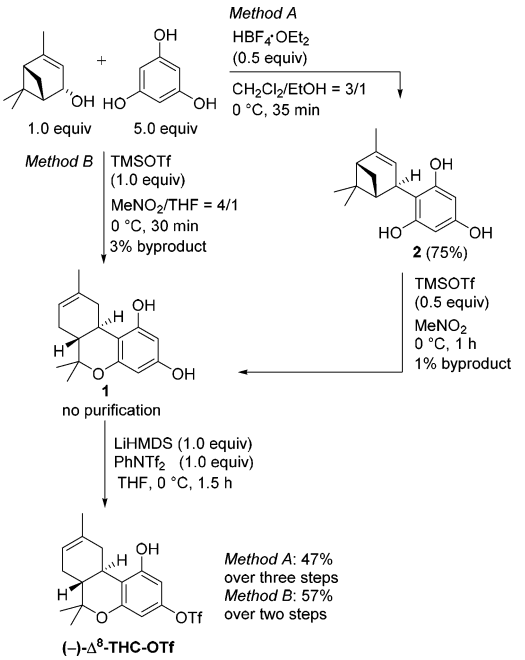


small *meta* substituents are attached to the resorcinol component, and the corresponding regioisomeric products were categorized as "abnormal" THCs.[12−14] For example, Antoniotti et al. used this "reversed" selectivity to prepare several *ortho*-THCs in flow.[15] To circumvent this regioselectivity problem and to access a general THC building block for late-stage diversification of the *para* position, we envisioned using the symmetric phloroglucinol as the resorcinol reaction component in such a cascade. Friedel–Crafts alkylation and O-cyclization should lead to the tetrahydrodibenzopyran product **1**. Since phloroglucinol is symmetric, the aromatic C–H sites do not have to be differentiated. In an additional synthetic step, the sterically less hindered phenolic OH-group in the *para* position should then be activated by selective triflation for the envisioned cross-coupling chemistry (Scheme 1, C).[16]

Phloroglucinol has already been used by other groups for the synthesis of THC derivatives.[16,17] However, to construct the tetrahydrodibenzopyran core structure in high yields, several synthetic steps were needed due to a complex protecting group strategy caused by the low solubility of phloroglucinol in the utilized organic solvents and due to separation issues of unreacted phloroglucinol. Moreover, the subsequent cross-coupling of the respective triflate required protection of the phenolic alcohol, which renders the overall synthesis of THC derivatives by such a sequence laborious.

We therefore commenced our studies by first investigating the solubility of phloroglucinol as this seemed to us to be the key to a short and efficient synthesis of (−)-Δ⁸-THC triflate. Extensive experimentation revealed that the Friedel–Crafts alkylation works best in a mixture of dichloromethane and ethanol (3/1; Scheme 2, method A). Double alkylation of

Scheme 2. (−)-Δ⁸-THC Triflate Can Be Synthesized in High Purity in Three Steps (Method A, 47% Yield) or Directly over Two Steps (Method B, 57%)



phloroglucinol was prevented by using a large excess of cheap phloroglucinol (5.0 equiv), which can easily be removed after the reaction by simple water extraction.

HPLC analysis showed that the isolated material contained several isomeric compounds with the same mass. Likely, different isomers are formed in the cascade under the applied conditions considering stereochemistry (*cis*/*trans*), double-bond position (Δ⁸/Δ⁹), and cyclized/noncyclized isomers. We did not succeed in isolating and characterizing all compounds by preparative HPLC. Since these impurities were also not separable at a later stage of the synthesis, we had to further optimize the protocol toward selective formation of intermediate **2**. Along with the solvent dependence, the cascade was sensitive to the reaction time. We found that by using $HBF_4{\cdot}OEt_2$ (0.5 equiv) in CH_2Cl_2/EtOH (3/1) at 0 °C the reaction can be stopped after 35 min at the stage of the bicylic product **2** (Scheme 2, method A), which was isolated in very good 75% yield by column chromatography containing traces (around 1%) of **1** as the only inseparable impurity (as checked by HPLC; see the SI). Selective ring closure to the tricyclic tetrahydrodibenzopyran was accomplished with TMSOTf as Lewis acid in $MeNO_2$[18] (TMSOTf 0.5 equiv, $MeNO_2$, 0 °C, 1 h), delivering **1** with high purity containing only around 1% of an inseparable isomer.

Since both steps toward **1** are acid catalyzed, we supposed that **1** may be accessible directly from verbenol and phloroglucinol (Scheme 2, method B) in a single operation. After renewed careful optimization of the amount of acid, solvent mixture, and reaction time (TMSOTf (1.0 equiv), $MeNO_2$/THF = 4/1, 0 °C, 30 min), **1** was directly obtained in high yield containing only 3% of an inseparable isomer (as

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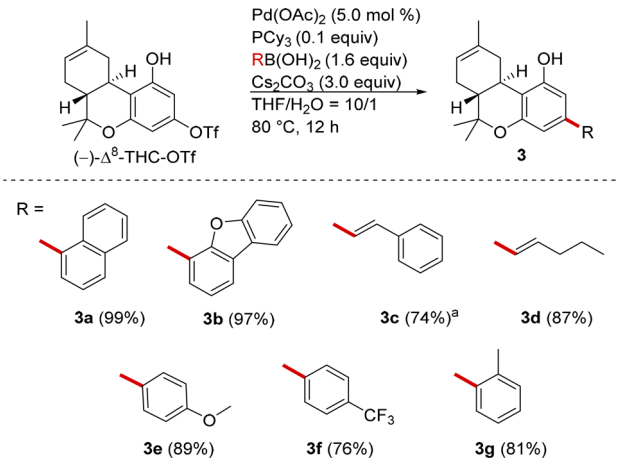
analyzed by HPLC, see the SI). Because the isolation of **1** turned out to be difficult at this stage of the synthesis, the crude product obtained via either method A or method B was directly used for the next step without any further purification.

Triflate activation of the phenolic alcohol was studied next. To avoid double triflation of both phenolic OH groups, 1 equiv of the sterically demanding reagent $PhNTf_2$ was used in combination with LiHMDS as the base (1 equiv). Double triflation could be suppressed, and (−)-Δ^8-THC-OTf was isolated in 47% over three steps using method A (1% isomer) and 57% over two steps applying method B (3% isomer).

The THC triflate building block was then applied to late-stage diversification by using the Suzuki−Miyaura reaction (Scheme 3).[19] Importantly, the cross-coupling proceeds

Scheme 3. Cross-Coupling Products of THC Triflate with Boronic Acids[a]



[a]With the potassium trifluoroborate salt instead of the boronic acid.

without protection of the phenolic alcohol group. Different pharmacologically interesting side chains were successfully coupled in good to high yields to the *para* position of the tetrahydrodibenzopyran core including bulky groups like dibenzofuranyl (**3b**), the naphthyl group leading to a highly active analogue (**3a**),[7a] electron-rich and -poor aromatic groups (**3e−g**), and side chains containing double bonds (**3c,d**), which are known to improve receptor binding properties due to their conformational restriction.[7b] The structures were confirmed by 2D NMR analysis (see SI) and for compound **3g** unambiguously by single-crystal X-ray analysis (Figure 2).

Focusing on the parent THC, the direct introduction of the pentyl side chain to the THC triflate building block to access (−)-Δ^8-THC via sp^2−sp^3 coupling turned out to be difficult. We tried various known protocols using Fe or Pd catalysis and obtained a disappointing 15% yield as the best result when the Stille coupling was applied. Since we obtained high yields for sp^2−sp^2 cross-couplings (see above), we decided to first install a pentenyl chain (**3d**, 87% yield). In a second step, the activated double bond next to the aromatic system was selectively hydrogenated in the presence of the second, higher substituted double bond within the tetrahydrodibenzopyran core using Pd/C (Scheme 4). Pleasingly, a good regioselectivity was achieved upon running the hydrogenation at −15 °C. If the cross-coupling product was directly used without further purification in the subsequent hydrogenation step,

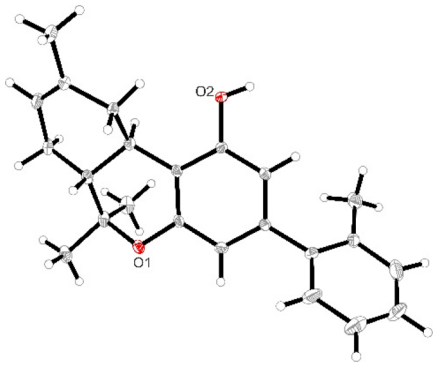
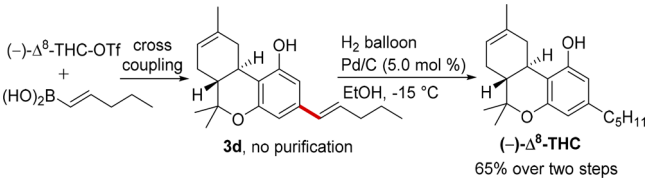


Figure 2. X-ray structure of compound **3g**.

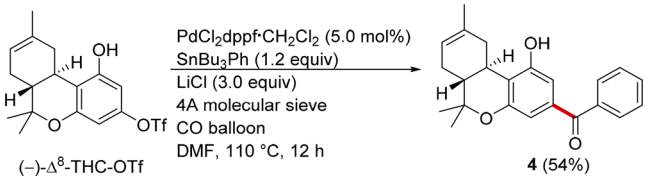
Scheme 4. Synthesis of (−)-Δ^8-THC Using the Readily Prepared THC Triflate Building Block



(−)-Δ^8-THC could be obtained in 65% over two steps and 37% total yield over four steps. In contrast to many terpenoid-based syntheses,[9] the herein presented protecting-group-free total synthesis of THC does not require the use of expensive olivetol to install the pentyl chain but utilizes cheap phloroglucinol and pentenyl boronic acid instead.

THC analogues bearing a benzoyl moiety are known to selectively interact with the CB_2 receptor.[16] Moreover, this group is capable of covalently labeling the receptor upon photoactivation, and THC molecules containing a carbonyl spacer also offer the opportunity for further modification into the corresponding 1,3-dithians, which are potent THC analogues, as shown by Makriyannis et al.[20] Along these lines, the THC triflate building block was successfully also used in a carbonylative Stille coupling to provide the benzoyl-substituted THC **4** in 54% yield without protection of the phenolic alcohol (Scheme 5). The overall yield to **4** from commercially available starting materials was 31% over three steps and competes well with the six-step synthesis of Moore.[21]

Scheme 5. Carbonylative Stille Coupling Delivers Benzoyl-Substituted THC



In summary, we synthesized *para* (−)-Δ^8-THC triflate as a general building block for late-stage introduction of THC side chains in two steps from commercially available starting materials in 57% yield. This building block was used in Suzuki−Miyaura cross-coupling reactions to access in high yields THC analogues bearing bulky side chains like naphthyl or dibenzofuranyl, aromatic moieties, or side chains containing double bonds. Furthermore, (−)-Δ^8-THC was synthesized

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from this building block in two steps and a total yield of 37% without the use of expensive olivetol. (−)-Δ^8-THC triflate can also be used in carbonylative Stille reactions to access benzoyl-substituted THC analogues. Importantly, no protecting groups are needed for the synthesis of our building block and for all investigated follow-up reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03907.

Experimental procedures, characterization data, ^{1}H and ^{13}C spectra, and X-ray data (PDF)

Accession Codes

CCDC 1883131 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) ElSohly, M. A.; Slade, D. *Life Sci.* **2005**, *78*, 539−548.

(2) Gaoni, Y.; Mechoulam, R. *J. Am. Chem. Soc.* **1964**, *86*, 1646−1647.

(3) (a) Matsuda, L. A.; Lolait, S. J.; Brownstein, M. J.; Young, A. C.; Bonner, T. I. *Nature* **1990**, *346*, 561−564. (b) Munro, S.; Thomas, K. L.; Abu-Shaar, M. *Nature* **1993**, *365*, 61−65. (c) Devane, W. A.; Dysarz, F. A.; Johnson, M. R.; Melvin, L. S.; Howlett, A. C. *Mol. Pharmacol.* **1988**, *34*, 605−613.

(4) Mallipeddi, S.; Janero, D. S.; Zvonok, N.; Makriyannis, A. *Biochem. Pharmacol.* **2017**, *128*, 1−11.

(5) Howlett, A. C.; Barth, F.; Bonner, T. I.; Cabral, G.; Casellas, P.; Devane, W. A.; Felder, C. C.; Herkenham, M.; Mackie, K.; Martin, B. R.; Mechoulam, R.; Pertwee, R. G. *Pharmacol. Rev.* **2002**, *54*, 161−202.

(6) Khanolkar, A. D.; Palmer, S. L.; Makriyannis, A. *Chem. Phys. Lipids* **2000**, *108*, 37−52.

(7) (a) Stern, E.; Lambert, D. M. *Chem. Biodiversity* **2007**, *4*, 1707−1728. (b) Papahatjis, D. P.; Nahmias, V. R.; Andreou, T.; Fan, P.; Makriyannis, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1616−1620.

(8) (a) Trost, B. M.; Dogra, K. *Org. Lett.* **2007**, *9*, 861−863. (b) Cheng, L.-J.; Xie, J.-H.; Chen, Y.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* **2013**, *15*, 764−767. (c) Gläser, F.; Bröhmer, M. C.; Hurrle, T.; Nieger, M.; Bräse, S. *Eur. J. Org. Chem.* **2015**, *2015*, 1516−1524. (d) Schafroth, M. A.; Zuccarello, G.; Krautwald, S.; Sarlah, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 13898−13901. (e) Shultz, Z. P.; Lawrence, G. A.; Jacobson, J. M.; Cruz, E. J.; Leahy, J. W. *Org. Lett.* **2018**, *20*, 381−384. (f) Klotter, F.; Studer, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 8547−8550.

(9) (a) Dethe, D. H.; Erande, R. D.; Mahapatra, S.; Das, S.; Kumar, V. B. *Chem. Commun.* **2015**, *51*, 2871−2873. (b) Razdan, R. K.; Dalzell, H. C.; Handrick, G. R. *J. Am. Chem. Soc.* **1974**, *96*, 5860−5865. (c) Petrzilka, T.; Haefliger, W.; Sikemeier, C.; Ohloff, G.; Eschenmoser, A. *Helv. Chim. Acta* **1967**, *50*, 719−723. (d) Mechoulam, R.; Braun, P.; Gaoni, Y. *J. Am. Chem. Soc.* **1967**, *89*, 4552−4554. (e) Razdan, R. K.; Handrick, G. R. *J. Am. Chem. Soc.* **1970**, *92*, 6061−6062. (f) Razdan, R. K.; Handrick, G. R.; Dalzell, H. C. *Experientia* **1975**, *31*, 16−17.

(10) (a) Hoffmann, G.; Studer, A. *Org. Lett.* **2018**, *20*, 2964−2966. (b) Hoffmann, G.; Studer, A. *Org. Lett.*, DOI: 10.1021/acs.orglett.8b03908.

(11) Westphal, M. V.; Schafroth, M. A.; Sarott, R. C.; Imhof, M. A.; Bold, C. P.; Leippe, P.; Dhopeshwarkar, A.; Grandner, J. M.; Katritch, V.; Mackie, K.; Trauner, D.; Carreira, E. M.; Frank, J. A. *J. Am. Chem. Soc.* **2017**, *139*, 18206−18212.

(12) Kraatz, U.; Korte, F. Z. *Z. Naturforsch., B: J. Chem. Sci.* **1976**, *31b*, 1382−1386.

(13) Crombie, L.; Crombie, W. M. L. *Phytochemistry* **1975**, *14*, 213−220.

(14) Uliss, D. B.; Handrick, G. R.; Dalzell, H. C.; Razdan, R. K. *Tetrahedron* **1978**, *34*, 1885−1888.

(15) Giorgi, P. D.; Liautard, V.; Pucheault, M.; Antoniotti, S. *Eur. J. Org. Chem.* **2018**, *2018* (11), 1307−1311.

(16) Dixon, D. D.; Tius, M. A.; Thakur, G. A.; Zhou, H.; Bowman, A. L.; Shukla, V. G.; Peng, Y.; Makriyannis, A. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5322−5325.

(17) Goanvic, D. L.; Tius, M. A. *J. Org. Chem.* **2006**, *71*, 7800−7804.

(18) Dixon, D. D.; Sethumadhavan, D.; Benneche, T.; Banaag, A. R.; Tius, M. A.; Thakur, G. A.; Bowman, A.; Wood, J. T.; Makriyannis, A. *J. Med. Chem.* **2010**, *53*, 5656−5666.

(19) Molander, G. A.; Petrillo, D. E.; Landzberg, N. R.; Rohanna, J. C.; Biolatto, B. *Synlett* **2005**, *11*, 1763−1766.

(20) Papahatjis, D. P.; Kourouli, T.; Abadji, V.; Goutopoulos, A.; Makriyannis, A. *J. Med. Chem.* **1998**, *41*, 1195−1200.

(21) Krishnamurthy, M.; Ferreira, A. M.; Moore, B. M., II *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3487−3490.

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