

Synthesis of Cannabidiols via Alkenylation of Cyclohexenyl Monoacetate

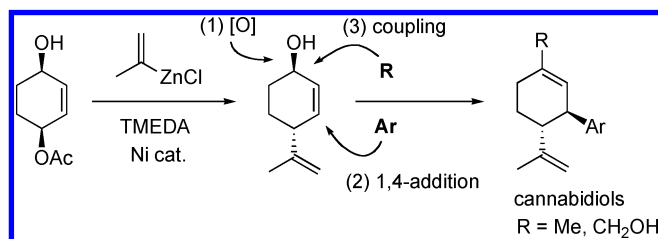
Yuichi Kobayashi,* Akira Takeuchi, and Yong-Gang Wang

Department of Biomolecular Engineering, Tokyo Institute of Technology,
4259 Nagatsuta-cho, Midori-ku, Yokohama 226-8501, Japan

ykobayas@bio.titech.ac.jp

Received March 21, 2006

ABSTRACT



Because of the lack of potency binding to the receptors responsible for psychoactivity, cannabidiol has received much attention as a lead compound to develop a nonpsychotropic drug. Herein, we establish a method to access not only cannabidiol but also its analogues. The key reaction is nickel-catalyzed allylation of 2-cyclohexene-1,4-diol monoacetate with a new reagent, (alkenyl)ZnCl/TMEDA, which gives a S_N2-type product with 94% regioselectivity in good yield.

After the finding of receptors (CB₁)¹ binding Δ⁹-tetrahydrocannabinol (Δ⁹-THC, **1**) (Figure 1),² biological study using cannabinoid analogues has led to the discovery of another subtype defined as CB₂.³ Both receptors are now believed to be responsible for the psychoactivity triggered by cannabis preparations such as hashish and marijuana.⁴ In contrast to **1**, cannabidiol (CBD, **2**), another constituent of the cannabis preparations, does not bind to the receptors,⁵ and in

consequence, **2** has received much attention as a lead compound to develop a nonpsychotropic drug. Moreover, recent studies have revealed other pharmacological properties such as antiinflammatory effects and activation of PPAR-γ.⁶ These aspects have created urgent demand for analogues as well as metabolites for further study.⁷

So far, **2** has been synthesized by several methods,^{8,9} among which the BF₃·OEt₂/Al₂O₃-promoted reaction^{9h} of the

(1) (a) Devane, W. A.; Dysarz, F. A., III; Hohnson, M. R.; Melvin, L. S.; Howlett, A. C. *Mol. Pharmacol.* **1988**, *34*, 605–613. (b) Matsuda, L. A.; Lolait, S. J.; Brownstein, M. J.; Young, A. C.; Bonner, T. I. *Nature* **1990**, *346*, 561–564. (c) Devane, W. A.; Hanus, L.; Breuer, A.; Pertwee, R. G.; Stevenson, L. A.; Griffin, G.; Gibson, D.; Mandelbaum, A.; Etinger, A.; Mechoulam, R. *Science* **1992**, *258*, 1946–1949.

(2) In this paper, two different numbering systems are adopted to indicate a specific site in the tricyclic and bicyclic cannabinoids to use the well-known abbreviations with the familiar numbers, for example, Δ⁹-THC (based on the dibenzopyran ring system) and 7-OH-CBD (based on the monoterpoid system), etc.

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

(4) (a) Tullo, A. *Chem. Eng. News* **2005**, *83*(25), 84. (b) Di Marzo, V.; Bifulco, M.; Petrocellis, L. D. *Nat. Rev. Drug Discovery* **2004**, *3*, 771–784. (c) Palmer, S. L.; Thakur, G. A.; Makriyannis, A. *Chem. Phys. Lipids* **2002**, *121*, 3–19. (d) Kunos, G.; Bátka, S.; Offertáler, L.; Mo, F.; Liu, J.; Karcher, J.; Harvey-White, J. *Chem. Phys. Lipids* **2002**, *121*, 45–56.

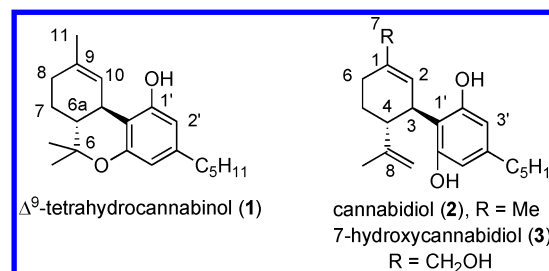


Figure 1. Representative examples of cannabinoids.

Table 1. Reaction of Isopropenyl Anions with Monoacetate **4**^a

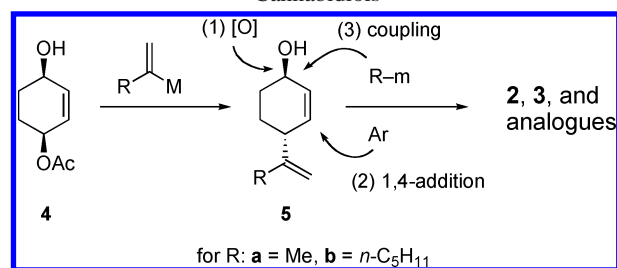
entry	reagent	reagent source (equiv)	additive(s) (equiv)	catalyst ^b	ratio ^c of 5a/11	yield, % ^d
1	7	6 (1.8), <i>n</i> -BuLi (2)	NaI (1), <i>t</i> -BuCN (5)	NiCl ₂ (tpp) ₂	67:33	46 ^e
2	8	8 (4)	—	CuCN	60:40	81
3	8	8 (4)	MgCl ₂ (15)	CuCN	86:14	90
4	9	8 (4), ZnCl ₂ (10)	—	CuCN	—	0
5	9	8 (4), ZnCl ₂ (10)	—	NiCl ₂ (tpp) ₂	67:33	31
6	9	8 (6), ZnCl ₂ (10)	TMEDA (10)	NiCl ₂ (tpp) ₂	92:8	95
7	9	8 (3.5), ZnCl ₂ (4)	TMEDA (4.2)	NiCl ₂ (tpp) ₂	94:6	85 (80) ^f
8	10	8 (6), ZnCl ₂ (2.5)	TMEDA (2.5)	NiCl ₂ (tpp) ₂	86:14	88

^a Reactions were carried out in THF at room temperature overnight (entries 1 and 4–8) or for 3 h (entries 2 and 3). ^b NiCl₂(tpp)₂ (20 mol %), CuCN (40 mol %). ^c Determined by ¹H NMR spectroscopy. ^d Combined yields determined by ¹H NMR spectroscopy with pyridine as a standard. ^e 2-Cyclohexenone was also coproduced in 15% yield. ^f Isolated yield.

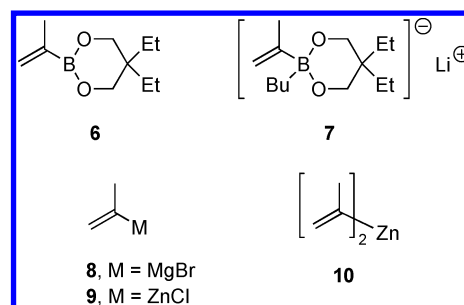
monoterpene with olivetol furnished **2** in a satisfactory manner. However, the methods would hardly be applicable to synthesis of structurally related analogues, especially those possessing a longer alkenyl side chain in place of the isopropenyl group.^{4,10} A recent seven-step oxidation¹¹ of the C(7) methyl group of **2** producing 7-hydroxy-CBD (**3**), a metabolite of **2**, also implies the unavailability of a synthetic route to the CBD family.

Recently, we reported an indirect method for installation of a bulky aromatic ring onto the γ -substituted cyclohexenone and subsequent generation of a reactive enolate.¹² By using this method, we synthesized **1** and its analogues successfully. However, the substituent we could place at the γ position of the cyclohexanone is limited to that derived by aldol reaction with an aldehyde. To gain wider flexibility in this method, we envisaged reaction of 2-cyclohexene-1,4-diol monoacetate **4**¹³ with alkenyl reagents furnishing compounds of type **5**, which would be transformed into the CBD family and related analogues by the method mentioned above (Scheme 1). A synthetic advantage of this strategy is availability of optically active **4** by the established method.¹³

Herein, we report a new reagent system for this purpose and a synthesis of **2** and CBD analogues.

Scheme 1. Synthetic Strategy Furnishing Bicyclic Cannabidiols

The present investigation was started with an application of the reagent systems originally developed for cyclopentene monoacetate.¹⁴ Thus, reaction of **4** with lithium isopropenyl borate **7**,¹⁵ prepared in situ from the boronate ester **6** and *n*-BuLi, proceeded at room temperature but afforded a mixture of products, among which the desired product **5a** (R = Me) and the regioisomer **11** were detected in moderate yield with a 67:33 ratio by ¹H NMR spectroscopy (Table 1, entry 1). Next we studied the CuCN-catalyzed reaction with



alkenyl Grignard reagents. According to the earlier result with 2-cyclopentene-1,4-diol monoacetate, isopropenylmagnesium *chloride* would be a suitable reagent for the present reaction with **4**.^{14c} However, preparation of the chloride reagent was unsuccessful as stated.^{14c} Instead, the *bromide* reagent **8**, prepared easily, resulted in lower regioselectivity

(5) Mechoulam, R.; Hanus, L. *Chem. Phys. Lipids* **2002**, *121*, 35–43.

(6) Sumariwalla, P. F.; Gallily, R.; Tchilibon, S.; Fride, E.; Mechoulam, R.; Feldmann, M. *Arthritis Rheum.* **2004**, *50*, 985–998.

(7) Mechoulam, R.; Parker, L. A.; Gallily, R. J. *Clin. Pharmacol.* **2002**, *42*, 11S–19S.

(8) Tius, M. A. *Stud. Nat. Prod. Chem.* **1997**, *19*, 185–244.

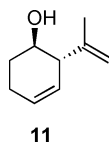
(9) (a) Mechoulam, R.; Gaoni, Y. *J. Am. Chem. Soc.* **1965**, *87*, 3273–3275. (b) Mechoulam, R.; Braun, P.; Gaoni, Y. *J. Am. Chem. Soc.* **1972**, *94*, 6159–6165. (c) Vaillancourt, V.; Albizati, K. F. *J. Org. Chem.* **1992**, *57*, 3627–3631. (d) Childers, W. E., Jr.; Pinnick, H. W. *J. Org. Chem.* **1984**, *49*, 5276–5277. (e) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582–7594. (f) Petrzilka, T.; Haefliger, W.; Sikemeier, G.; Ohloff, G.; Eschenmoser, A. *Helv. Chim. Acta* **1967**, *719*–723. (g) Razdan, R. K.; Dalzell, H. C.; Handrick, G. R. *J. Am. Chem. Soc.* **1974**, *96*, 5860–5865. (h) Baek, S.-H.; Srebnik, M.; Mechoulam, R. *Tetrahedron Lett.* **1985**, *26*, 1083–1086. (i) Hanus, L. O.; Tchilibon, S.; Ponde, D. E.; Breuer, A.; Fride, E.; Mechoulam, R. *Org. Biomol. Chem.* **2005**, *3*, 1116–1123.

(10) (a) Tius, M. A.; Busch-Petersen, J.; Marris, A. R. *Chem. Commun.* **1997**, 1867–1868. (b) Drake, D. J.; Jensen, R. S.; Busch-Petersen, J.; Kawakami, J. K.; Fernandez-Garcia, M. C.; Fan, P.; Makriyannis, A.; Tius, M. A. *J. Med. Chem.* **1998**, *41*, 3596–3608. (c) Harrington, P. E.; Stergiades, I. A.; Erickson, J.; Makriyannis, A.; Tius, M. A. *J. Org. Chem.* **2000**, *65*, 6576–6582. (d) Chu, C.; Ramamurthy, A.; Makriyannis, A.; Tius, M. A. *J. Org. Chem.* **2003**, *68*, 55–61 and references therein.

(11) Tchilibon, S.; Mechoulam, R. *Org. Lett.* **2000**, *2*, 3301–3303.

(12) (a) William, A. D.; Kobayashi, Y. *Org. Lett.* **2001**, *3*, 2017–2020; *J. Org. Chem.* **2002**, *67*, 8771–8782.

(entry 2). The incompatibility between the reagent preparation and the regioselectivity was overcome by addition of excess MgCl_2 , which afforded an improved ratio of 86:14 and a good combined yield (entry 3). In addition, separation of the regioisomers **5a** and **11** by silica gel column chromatography was an easy task.



Although the result of entry 3 might be practical, we next explored reaction with zinc reagents to attain a better selectivity. Thus, zinc reagent **9** (4 equiv), prepared from **8** and excess ZnCl_2 , was subjected to reaction with **4** in the presence of CuCN or $\text{NiCl}_2(\text{tpp})_2$ (tpp/PPh_3) as a catalyst (entries 4 and 5). Among the catalysts, $\text{NiCl}_2(\text{tpp})_2$ afforded products **5a** and **11** but in lower regioselectivity and in lower yield. Fortunately, addition of TMEDA improved the regioselectivity and reactivity to afford **5a** in good yield (entry 6). Use of smaller quantities of the reagents and TMEDA also provided good results with 80% isolated yield (entry 7). In contrast, the reagent prepared from **8** and ZnCl_2 in a 2:1 ratio, probably **10**, was inferior in regioselectivity (entry 8).

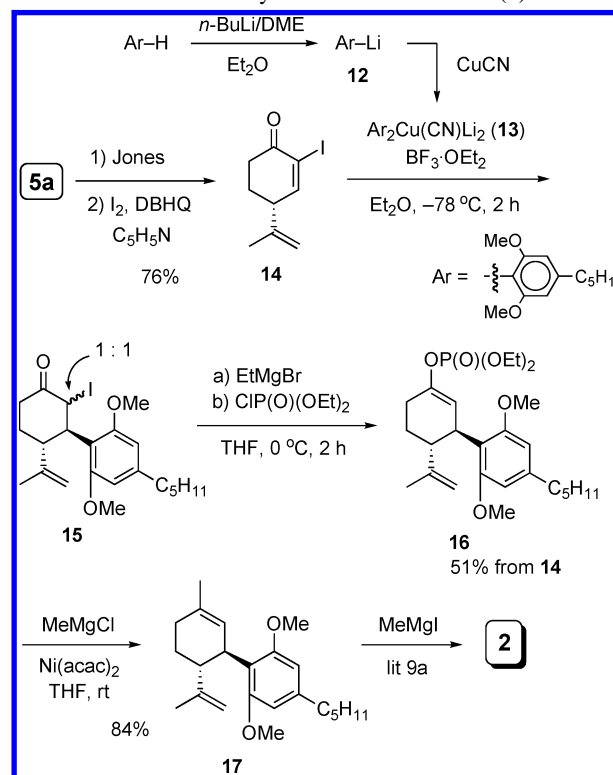
Product **5a** was transformed successfully into the dimethyl ether of CBD (Scheme 2). Oxidation of **5a** afforded an enone, which underwent iodination at the α position by I_2 in the presence of 2,5-di-*tert*-butylhydroquinone (DBHQ) as a radical scavenger to produce α -iodo enone **14** in 63% yield (two steps). Addition of the 2,6-dimethoxy-4-pentylphenyl group (abbreviated as Ar in the scheme) to enone **14** was performed with the higher-order cyanocuprate **13** derived from the lithium anion **12** and CuCN according to our previous procedure¹² with modification.¹⁶ Compound **15**, obtained as a 1:1 stereoisomeric mixture at the α position, underwent reaction with EtMgBr ¹⁷ to produce the reactive magnesium enolate, which was quenched with $\text{CIP}(=\text{O})(\text{OEt})_2$ to furnish enol phosphate **16** in 51% yield from **14**. Nickel-catalyzed coupling of **16** with MeMgCl afforded dimethyl ether **17** in good yield. The ^1H and ^{13}C NMR spectra of synthetic **17** were identical with the data published.^{9c,i} Demethylation of **17** using MeMgI to CBD (**2**) and demethylation/cyclization to Δ^9 -THC (**1**) have been reported in the literature.^{9a,d}

(13) (a) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656–2665. (b) Harris, K. J.; Gu, Q.-M.; Shih, Y.-E.; Girdaukas, G.; Sih, C. J. *Tetrahedron Lett.* **1991**, *32*, 3941–3944. (c) Bäckvall, J.-E.; Gatti, R.; Schink, H. E. *Synthesis* **1993**, 343–348. (d) López-Pelegrín, J. A.; Janda, K. D. *Chem.–Eur. J.* **2000**, *6*, 1917–1922. (e) Suzuki, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **2001**, *66*, 1494–1496. (f) Hua, Z.; Yu, W.; Su, M.; Jin, Z. *Org. Lett.* **2005**, *7*, 1939–1942.

(14) (a) Review: Kobayashi, Y. *Curr. Org. Chem.* **2003**, *7*, 133–147. (b) Nakata, K.; Kobayashi, Y. *Org. Lett.* **2005**, *7*, 1319–1322. (c) Kobayashi, Y.; Nakata, K.; Aina, T. *Org. Lett.* **2005**, *7*, 183–186. (d) Kobayashi, Y.; Muruges, M. G.; Nakano, M.; Takahisa, E.; Usmani, S. B.; Aina, T. *J. Org. Chem.* **2002**, *67*, 7110–7123.

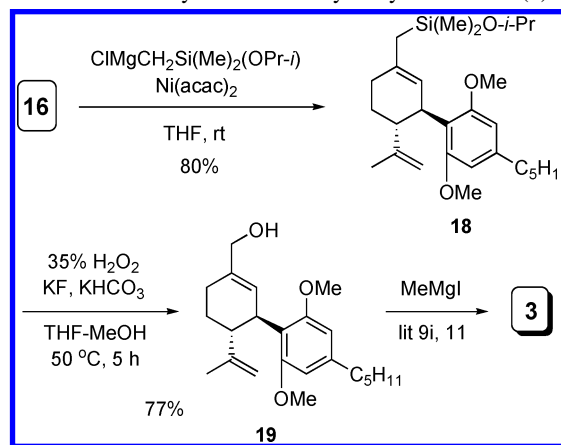
(15) The highly volatile nature of the isopropenyl boronate ester with the original 2,3-butanediol ligand prevented its isolation, whereas compound **6**, studied herein, was less volatile.

Scheme 2. Synthesis of Cannabidiol (**2**)



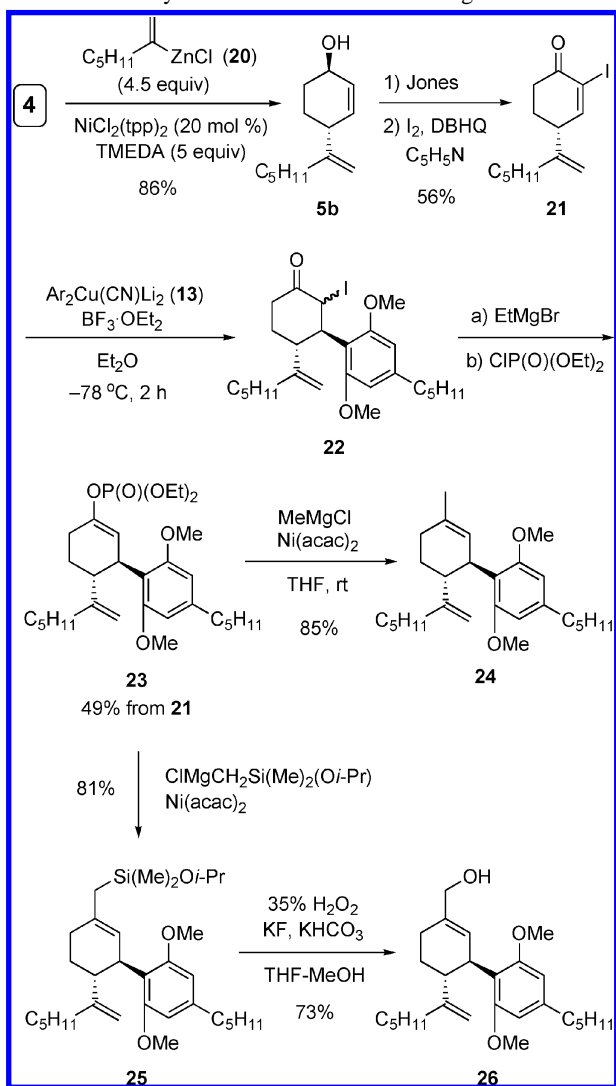
Synthesis of the dimethyl ether **19**, the known precursor of 7-hydroxy-CBD (**3**),^{9i,11} was achieved commencing with enol phosphate **16** as summarized in Scheme 3. Thus, nickel-

Scheme 3. Synthesis of 7-Hydroxycannabidiol (**3**)



catalyzed reaction with $\text{ClMgCH}_2\text{Si}(\text{Me})_2(\text{OPr-}i)$ afforded the coupling product **18** in 80% yield, which upon Tamao oxidation¹⁸ produced alcohol **19**^{9i,11} in good yield.

We then turned our attention to the synthesis of analogues possessing a longer alkenyl chain in place of the isopropenyl group because the isopropenyl moiety is an important pharmacophore to control the biological property.^{4,10} The $\text{CH}_2=\text{C}(\text{C}_5\text{H}_{11})$ group was chosen as a typical example. Thus,

Scheme 4. Synthesis of Cannabidiol Analogues **23** and **25**

$\text{CH}_2=\text{C}(\text{C}_5\text{H}_{11})\text{ZnCl}$ (**20**) was prepared from $\text{CH}_2=\text{C}(\text{C}_5\text{H}_{11})\text{-MgBr}$ and ZnCl_2 and subjected to reaction with monoacetate

4 in the presence of $\text{NiCl}_2(\text{tpp})_2$ as a catalyst to afford **5b** in 86% yield with a 94:6 regioisomeric ratio¹⁹ (Scheme 4). Alcohol **5b** was converted to enol phosphate **23** in the same manner as **5a** was transformed to **16**. Finally, coupling of **23** with MeMgCl afforded **24**, and coupling with $\text{ClMgCH}_2\text{-Si}(\text{Me})_2(\text{OPr-}i)$ followed by Tamao oxidation¹⁸ of the resulting **25** furnished **26** in 60% yield over two steps.

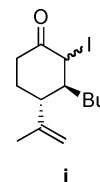
In summary, we have developed a new way to prepare cannabinoids starting with monoacetate **4**, in which regioselective installation of an alkenyl group to the cyclohexenyl ring of **4** is accomplished with a new reagent system consisting of (alkenyl)ZnCl, TMEDA, and $\text{NiCl}_2(\text{tpp})_2$ (cat.). Application of this reagent to other allylic substrates is under investigation.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

Supporting Information Available: Experimental procedures and spectral data for compounds described herein. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL060692H

(16) Because we had occasionally experienced insufficient lithiation of the dimethyl ether of olivetol (Ar-H in Scheme 2) with $n\text{-BuLi}$ in Et_2O , thus producing a mixture of **15** and the Bu group incorporated product **i**, we reinvestigated this step with or without any additive. We now recommend a procedure of stirring the olivetol ether (Ar-H) in Et_2O with $n\text{-BuLi}$ (1.2 equiv) and DME (2.4 equiv) at room temperature for 2 h. Other conditions attempted are presented in the Supporting Information.



(17) Aoki, Y.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1995**, 463–464.

(18) Tamao, K.; Ishida, N. *Tetrahedron Lett.* **1984**, 25, 4245–4248.

(19) The reagent system with $\text{CH}_2=\text{CH}(\text{C}_5\text{H}_{11})\text{MgBr}$ (3.5 equiv), CuCN (30 mol %), and MgCl_2 (10 equiv) in THF afforded a 77:23 mixture of **5b** and its regioisomer quantitatively.