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Synthesis of Cannabidiols via Alkenylation of Cyclohexenyl Monoacetate

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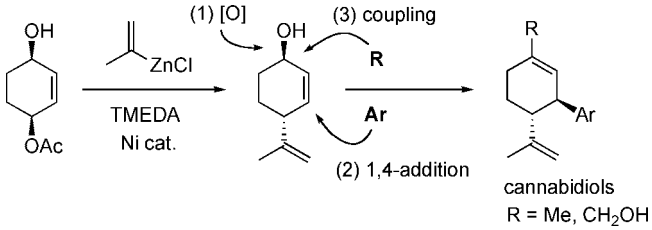
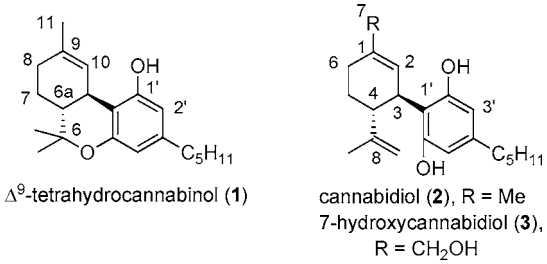
ABSTRACT



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 (CB_1)[1] binding Δ^9-tetrahydrocannabinol (Δ^9-THC, **1**) (Figure 1),[2] biological study using cannabinoid analogues has led to the discovery of another subtype defined as CB_2.[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 $BF_3{\cdot}OEt_2/Al_2O_3$-promoted reaction[9h] of the



Δ9-tetrahydrocannabinol (**1**)

cannabidiol (**2**), R = Me
7-hydroxycannabidiol (**3**),
R = CH_2OH

Figure 1. Representative examples of cannabinoids.

(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, Δ^9-THC (based on the dibenzopyran ring system) and 7-OH-CBD (based on the monoterpenoid 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.; Bátkai, S.; Offertáler, L.; Mo, F.; Liu, J.; Karcher, J.; Harvey-White, J. *Chem. Phys. Lipids* **2002**, *121*, 45−56.

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

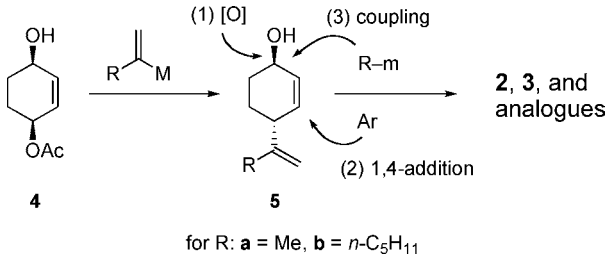
entry	reagent	reagent source (equiv)	additive(s) (equiv)	catalyst[b]	ratio[c] of **5a/11**	yield, %[d]
1	**7**	**6** (1.8), *n*-BuLi (2)	NaI (1), *t*-BuCN (5)	$NiCl_2(tpp)_2$	67:33	46[e]
2	**8**	**8** (4)	—	CuCN	60:40	81
3	**8**	**8** (4)	$MgCl_2$ (15)	CuCN	86:14	90
4	**9**	**8** (4), $ZnCl_2$ (10)	—	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] $NiCl_2(tpp)_2$ (20 mol %), CuCN (40 mol %). [c] Determined by ^{1}H NMR spectroscopy. [d] Combined yields determined by ^{1}H NMR spectroscopy with pyridine as a standard. [e] 2-Cyclohexenone was also coproduced in 15% yield. [f] Isolated yield.

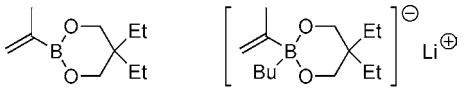
monoterpene with olivetol furnished **2** in a satisfactory manner. However, the methods would hardly be applicable to synthesis of structurally related analogues, especially those possessing a longer alkenyl side chain in place of the isopropenyl group.[4,10] A recent seven-step oxidation[11] of the 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 ^{1}H NMR spectroscopy (Table 1, entry 1). Next we studied the CuCN-catalyzed reaction with



6 **7**

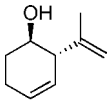
8, M = MgBr
9, M = ZnCl

10

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.

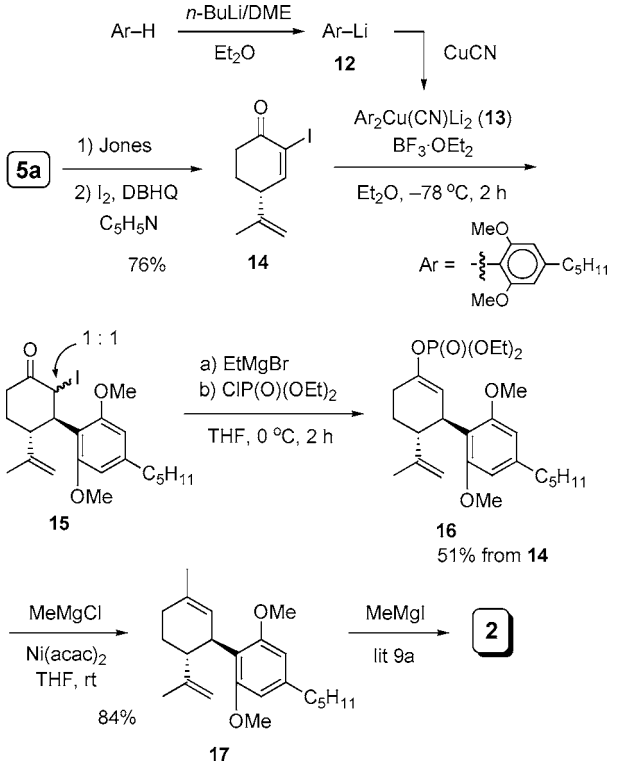


11

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 $NiCl_2(tpp)_2$ (tpp/PPh_3) as a catalyst (entries 4 and 5). Among the catalysts, $NiCl_2(tpp)_2$ 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).

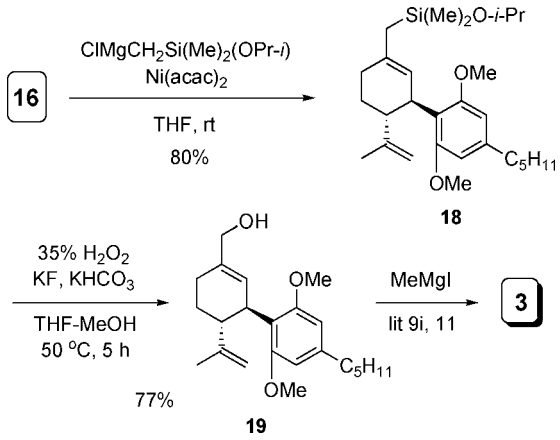
Product **5a** was transformed successfully into the dimethyl ether of CBD (Scheme 2). Oxidation of **5a** afforded an enone, which underwent iodination at the α position by I_2 in the presence of 2,5-di-*tert*-butylhydroquinone (DBHQ) as a radical scavenger to produce α-iodo enone **14** in 63% yield (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 procedure[12] 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 ClP(=O)-$(OEt)_2$ 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]

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 $ClMgCH_2Si(Me)_2(OPr\text{-}i)$ afforded the coupling product **18** in 80% yield, which upon Tamao oxidation[18] produced alcohol **19**[9i,11] in good yield.

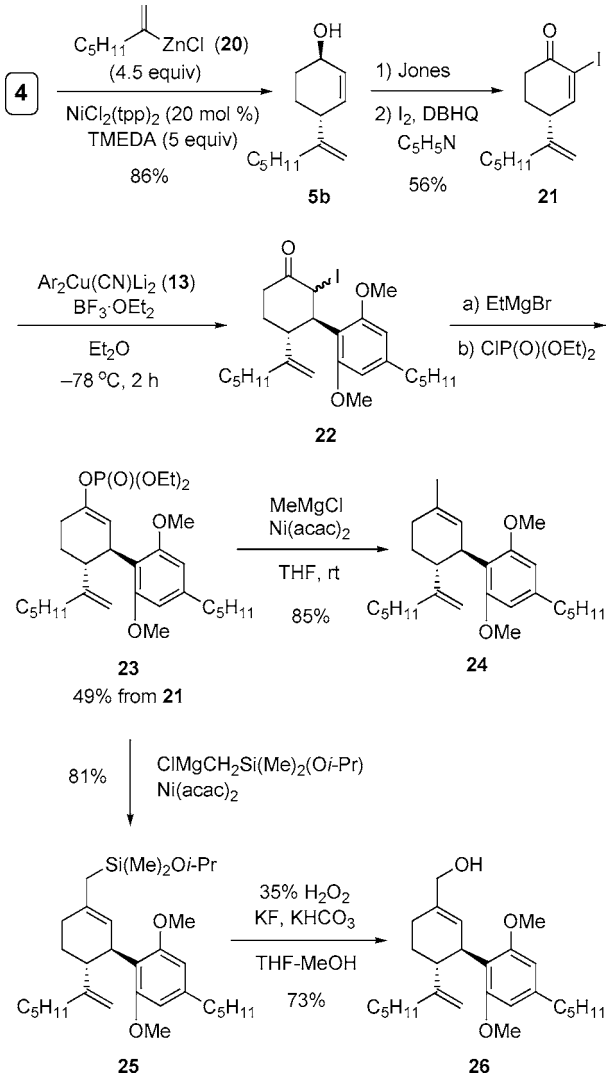
We then turned our attention to the synthesis of analogues possessing a longer alkenyl chain in place of the isopropenyl group because the isopropenyl moiety is an important pharmacophore to control the biological property.[4,10] The $CH_2{=}C(C_5H_{11})$ group was chosen as a typical example. Thus,

(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.; Ainai, T. *Org. Lett.* **2005**, *7*, 183−186. (d) Kobayashi, Y.; Murugesh, M. G.; Nakano, M.; Takahisa, E.; Usmani, S. B.; Ainai, 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 4. Synthesis of Cannabidiol Analogues **23** and **25**



$CH_2{=}C(C_5H_{11})ZnCl$ (**20**) was prepared from $CH_2{=}C(C_5H_{11})$-MgBr and $ZnCl_2$ and subjected to reaction with monoacetate **4** in the presence of $NiCl_2(tpp)_2$ as a catalyst to afford **5b** in 86% yield with a 94:6 regioisomeric ratio[19] (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 $ClMgCH_2$-$Si(Me)_2(OPr\text{-}i)$ followed by Tamao oxidation[18] 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 $NiCl_2(tpp)_2$ (cat.). Application of this reagent to other allylic substrates is under investigation.

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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.

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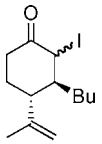
(16) Because we had occasionally experienced insufficient lithiation of the dimethyl ether of olivetol (Ar−H in Scheme 2) with *n*-BuLi in Et_2O, thus producing a mixture of **15** and the Bu group incorporated product **i**, we reinvestigated this step with or without any additive. We now recommend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



i

(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 $CH_2{=}CH(C_5H_{11})MgBr$ (3.5 equiv), CuCN (30 mol %), and $MgCl_2$ (10 equiv) in THF afforded a 77:23 mixture of **5b** and its regioisomer quantitatively.