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Efficient one-pot synthetic approaches for cannabinoid analogues and their application to biologically interesting (−)-hexahydrocannabinol and (+)-hexahydrocannabinol

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Abstract

This Letter reports new and efficient synthetic approaches for biologically interesting cannabinoid analogues. The key strategies involve ethylenediamine diacetate/triethylamine-catalyzed cyclization. As an application of this methodology, one-step synthesis of biologically active natural (−)-hexahydrocannabinol and its unnatural enantiomer (+)-hexahydrocannabinol was carried out.

Keywords: Cannabinoid; Ethylenediamine diacetate/triethylamine; Hetero Diels–Alder reaction; (−)-Hexahydrocannabinol; (+)-Hexahydrocannabinol

1. Introduction

Cannabinoids are widely distributed in nature and have been isolated from the Indian hemp *Cannabis sativa*, which has been used as both a medicine and a psychotomimetic drug since ancient times.[1] These compounds have been shown to possess analgesic, antiemetic, psychotropic, and anti-inflammatory properties.[2] They also have shown their potential therapeutic utility for the treatment of asthma and glaucoma.[3] The medical use of cananabinoids as therapeutic agents has been limited by their psychotropic properties.[4] However, the discovery of the two cannabinoid receptors, CB1 and CB2, has ushered in a new era in research for the development of drugs.[5] Among these, Δ^8-tetrahydrocannabinol (**1**) (Δ^8-THC) and Δ^9-tetrahydrocannabinol (**2**) (Δ^9-THC) are the major psychopharmacological active constituents of marijuana (hashish) (Fig. 1).[6] Their analogues have also attracted medical interest because they show promising biological and pharmacological activities including antiemetic, analgesic, and psychotropic effects.[7] In particular, enantiomerically pure (−)-hexahydrocannabinol (**3**) has attracted considerable attention since clinical tests showed these compounds to have similar psychotropic activity to that of natural Δ^8-tetrahydrocannabinol (**1**).[8] Currently, synthesized Δ^9-tetrahydrocannabinol (**2**) (Δ^9-THC) and its derivative have been used as medicines, Marinol® and Cesamet®, for patients with chemotherapy-induced nausea and vomiting (CINV) who have failed to respond adequately to conventional antiemetic treatments.[9]

Recently, we developed a new and useful methodology for preparing a variety of benzopyrans using the ethylenediamine diacetate (EDDA)-catalyzed reactions of resorcinols to α,β-unsaturated aldehydes (Scheme 1).[10] These reactions involve a formal [3+3]cycloaddition through 6π-electrocyclization.[11] This methodology provides a rapid route for the synthesis of benzopyran derivatives with a variety of substituents on the pyranyl ring.[12]

As a part of an ongoing study into the synthetic efficacy of this methodology, this study examined the reactions of resorcinols or naphthols with optically pure citronellal. This reaction appears to be an ideal method for the synthesis of enantiomerically pure molecules with cannabinoid

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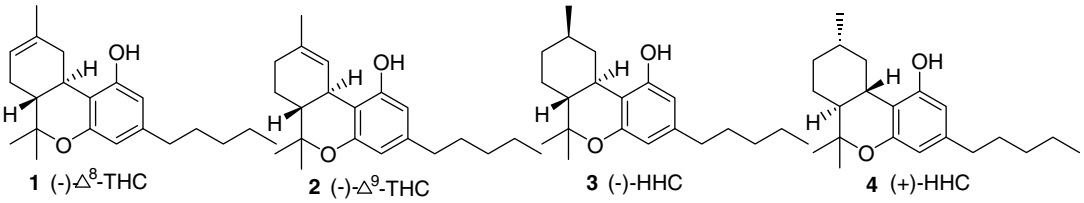
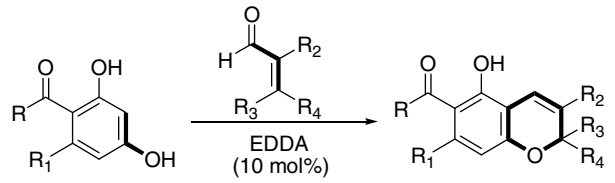


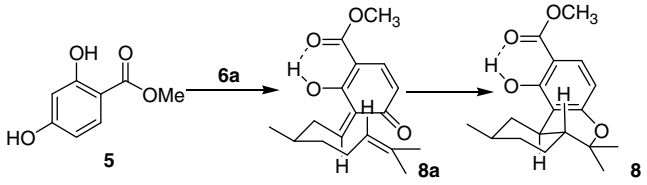
Fig. 1. Selected biologically interesting natural and unnatural cannabinoid.

moiety. We report an efficient one-pot synthesis of biologically interesting cannabinoid analogues. In addition, the one-step synthesis of natural (−)-hexahydrocannabinol and its unnatural enantiomer (+)-hexahydrocannabinol is reported as an application of this methodology.

The reaction of methyl 2,4-dihydroxybenzoate (**5**) (1 mmol) with (*R*)-(+)-citronellal (**6a**) ($[\alpha]_D$ +14.1, *c* 1.0, $CHCl_3$, 98% ee) was first investigated (Table 1). Indium(III) chloride (10 mol %) as a Lewis acid catalyst in refluxing acetonitrile did not produce any adducts, whereas ytterbium(III) triflate (10 mol %) afforded products **7** (8%) and **8** (3%) in very low yield. No products were obtained using pyridine as the reactant and solvent at 140 °C for 24 h. Treatment of compound **5** (1 mmol) with 20 mol % of ethylenediamine diacetate in refluxing xylene for 24 h gave the uncyclized and cyclized products **7** and **8** in 30% and 40% yields, respectively, whereas the reaction with triethylamine in refluxing xylene for 24 h afforded compounds **7** and **8** in 10% and 30% yields, respectively. The stereochemistry of the double bond of compound **7** was confirmed as *E* by the coupling constant ($J = 16.6$ Hz) from the ^{1}H NMR spectrum.[13] Interestingly, only the cyclized product **8** was obtained in 85% yield with ethylenediamine diacetate (20 mol %)/triethylamine (2 mL) as co-catalysts in refluxing xylene for 24 h.[14] The specific rotation value of compound **8** was $[\alpha]_D$ −127.7 (*c* 0.30, $CHCl_3$). The stereospecificity of compound **8** may be explained by a pseudoequatorial conformation of *o*-quinone methide **8a** for the coplanar structure adopted by the methyl group in the chair-like transition state, as shown Scheme 2. During hetero Diels–Alder reaction of *o*-quinone methide **8a**, the *exo*-transition state must have been more energetically favorable than the *endo*-transition state. A preference for *exo*-transition state was observed during the intramolecular hetero Diels–Alder reaction of *o*-quinone methide.[15] The regiospecificity of the sole product **8** may be due to hydrogen bond between the hydroxy group and carbonyl group of methyl ester. Therefore, cyclization of compound **5** is likely to occur on the position without a hydrogen bond. Compound **8** was easily separated by column chromatography and the assignment of its stereochemistry was readily confirmed by spectroscopic analyses.[14] Interestingly, treatment of **7** with ethylenediamine diacetate

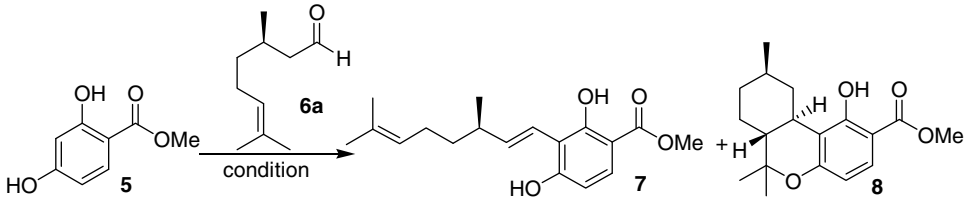


Scheme 1. Benzopyran formation by [3+3]cycloaddition reaction.



Scheme 2.

Table 1
Reaction of **5** with (*R*)-(+)-citronellal under several conditions

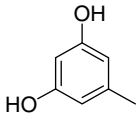
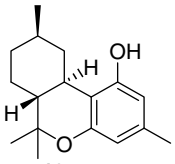
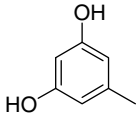
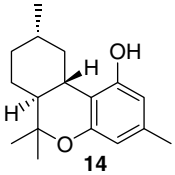
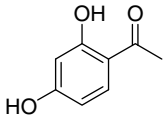
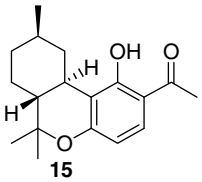
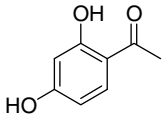
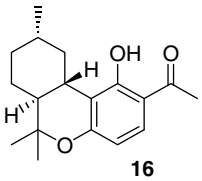
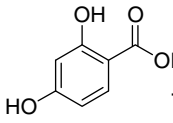
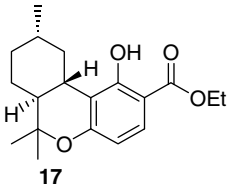
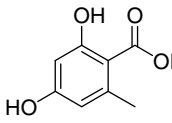
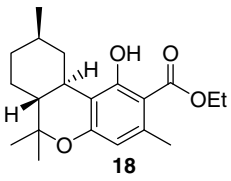
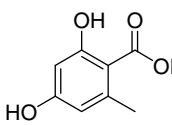
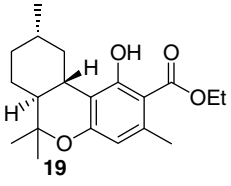


Condition		Yield (%)	
		7	**8**
$InCl_3$ (10 mol %)	Acetonitrile, reflux, 12 h	0	0
$Yb(OTf)_3$ (10 mol %)	Acetonitrile, reflux, 12 h	8	3
Pyridine (excess)	140 °C, 24 h	0	0
EDDA (20 mol %)	Xylene, reflux, 24 h	30	40
TEA (2 mL)	Xylene, reflux, 24 h	10	30
EDDA (20 mol %)/TEA (2 mL)	Xylene, reflux, 24 h	0	85

(20 mol %)/triethylamine (2 mL) in refluxing xylene for 12 h gave product **8** in 90% yield.

Additional reactions of several types of resorcinols with (*R*)-(+)-citronellal (**6a**) or (*S*)-(−)-citronellal (**6b**) ([α]$_D$ −15.0, neat) were carried out in the presence of ethylenediamine diacetate (20 mol %)/triethylamine (2 mL) in xylene. The results are shown in Table 2. A reaction of orcinol (**9**) with (*R*)-(+)-citronellal (**6a**) in refluxing xylene for 24 h afforded adduct **13** in 68% yield, whereas a reaction with (*S*)-(−)-citronellal (**6b**) afforded product **14** in 70% yield (entries 1 and 2). A higher yield of products was produced in the case of resorcinol with a carbonyl group on the benzene ring. For example, reaction of 2,4-dihydroxyacetophenone (**10**) with (*R*)-(+)-citronellal (**6a**) in refluxing

Table 2
Reactions of resorcinols with (*R*)-(+)-citronellal (**6a**) and (*S*)-(−)-citronellal (**6b**)[a]

Entry	Starting material	Aldehyde	Time (h)	Product	Yield (%)	$[\alpha]_D^{20}$
1	 **9**	**6a**	24	 **13**	68	−90.9 (*c* 0.18, $CHCl_3$)
2	 **9**	**6b**	24	 **14**	70	+94.5 (*c* 0.20, $CHCl_3$)
3	 **10**	**6a**	16	 **15**	75	−118.6 (*c* 0.25, $CHCl_3$)
4	 **10**	**6b**	16	 **16**	76	+123.4 (*c* 0.30, $CHCl_3$)
5	 **11**	**6b**	12	 **17**	84	+142.3 (*c* 0.30, $CHCl_3$)
6	 **12**	**6a**	12	 **18**	87	−130.6 (*c* 0.30, $CHCl_3$)
7	 **12**	**6b**	12	 **19**	86	+135.5 (*c* 0.30, $CHCl_3$)

[a] Conditions: starting material (1.0 mmol) and aldehyde (1.5 mmol) in refluxing xylene.

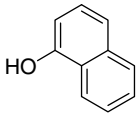
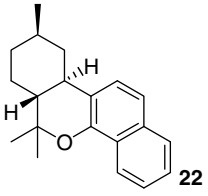
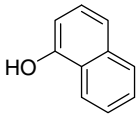
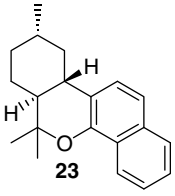
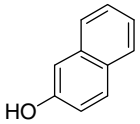
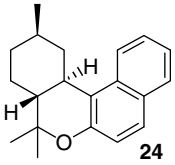
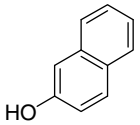
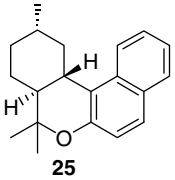
xylene gave compound **15** in 75% yield, whereas treatment with (*S*)-(−)-citronellal (**6b**) gave product **16** in 76% yield (entries 3 and 4). The cycloaddition reactions were successful with other resorcinols, including ester groups on the benzene ring. Reactions of ethyl 2,4-dihydroxybenzoate (**11**) and ethyl 2,4-dihydroxy-6-methylbenzoate (**12**) with (*R*)-(+)-citronellal (**6a**) or (*S*)-(−)-citronellal (**6b**) afforded the corresponding products **17**–**19** in 84%, 87%, and 86% yields, respectively (entries 5–7). These reactions provide a rapid route for the synthesis of cannabinoid derivatives with a variety of substituents on the benzopyran ring.

In an attempt to extend the utility of this methodology, further reactions with naphthols were examined as shown in Table 3. A reaction of 1-naphthol (**20**) with (*R*)-(+)-citronellal (**6a**) under EDDA/TEA in refluxing xylene for 8 h afforded compound **22** in 92% yield (entry 1).[16] Similarly, adduct **23** was obtained by a reaction with (*S*)-(−)-citronellal (**6b**) in refluxing xylene in 90% yield (entry 2). In the case of 2-naphthol (**21**), the desired products **24** and **25** were produced in 72% and 75% yields, respectively (entries 3 and 4).[17]

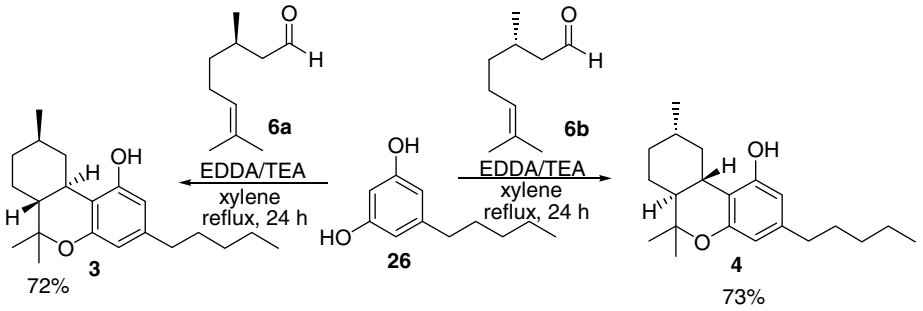
As an application of this methodology, a one-step synthesis of natural (−)-hexahydrocannabinol (**3**) and its unnatural (+)-hexahydrocannabinol (**4**) was next attempted. The total synthesis of (−)-hexahydrocannabinol (**3**) and (+)-hexahydrocannabinol (**4**) has already been reported by other groups. The synthesis of (−)-hexahydrocannabinol (**3**) was first accomplished by Tietze using an intramolecular Diels–Alder reaction of 1,3-cyclohexanedione followed by aromatization throughout a 3-step reaction.[18] Other syntheses of (−)-hexahydrocannabinol (**3**) and (+)-hexahydrocannabinol (**4**) was reported by Marino starting from olivetol monomethyl ether in a 5-step reaction.[19] (−)-Hexahydrocannabinol (**3**) and (+)-hexahydrocannabinol (**4**) were also synthesized by Cornia using diethylaluminium chloride-mediated condensation of olivetol with (*R*)-(+)- or (*S*)-(−)-citronellal.[20] Another synthetic approach to (−)-hexahydrocannabinol (**3**) was accomplished by Inoue from protected olivetol through a lithiation reaction followed by cyclization.[21] Although there are several methods available to synthesize (−)-hexahydrocannabinol (**3**) and (+)-hexahydrocannabinol (**4**) through the literature,[18–21] there is still a demand for general methods that can efficiently provide.

Scheme 3 shows an efficient one-step synthetic approach for natural (−)-hexahydrocannabinol (**3**) and its unnatural (+)-hexahydrocannabinol (**4**). A reaction of olivetol (**26**) with (*R*)-(+)-citronellal (**6a**) in the presence of ethylenediamine diacetate (20 mol %)/triethylamine (2 mL) in refluxing xylene for 24 h gave the natural (−)-hexahydrocannabinol (**3**) in 72% yield, whereas treatment with

Table 3
Reactions of naphthols with (*R*)-(+)-citronellal (**6a**) and (*S*)-(−)-citronellal (**6b**)[a]

Entry	Starting material	Aldehyde	Time (h)	Product	Yield (%)	$[\alpha]_D^{20}$
1	 **20**	**6a**	8	 **22**	92	−57.9 (*c* 1.02, $CHCl_3$)
2	 **20**	**6b**	8	 **23**	90	+60.5 (*c* 1.10, $CHCl_3$)
3	 **21**	**6a**	12	 **24**	72	−55.6 (*c* 0.50, $CHCl_3$)
4	 **21**	**6b**	12	 **25**	75	+56.1 (*c* 0.40, $CHCl_3$)

[a] Conditions: starting material (1.0 mmol) and aldehyde (1.5 mmol) in refluxing xylene.



Scheme 3.

(*S*)-(−)-citronellal (**6b**) for 24 h afforded the unnatural product **4** in 73% yield. The specific rotation value of compound **3** was $[\alpha]_D$ −85.4 (*c* 0.30, $CHCl_3$), whereas that of compound **4** was $[\alpha]_D$ +86.9 (*c* 0.10, $CHCl_3$).[22] The spectroscopic data of compounds **3** and **4** were in agreement with the reported data.[19]

In conclusion, a new and efficient synthetic route for biologically interesting cannabinoids was developed starting from commercially available resorcinols and optically pure citronellals utilizing the hetero Diels–Alder reaction as the key step. This synthetic route provided the biologically interesting natural (−)-hexahydrocannabinol (**3**) and its unnatural (+)-hexahydrocannabinol (**4**).

Acknowledgments

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13. *Spectral data for compound* **7**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.35 (1H, s), 7.70–7.50 (2H, m), 6.43 (1H, d, $J = 16.6$ Hz), 6.07 (1H, dd, $J = 16.6$, 7.8 Hz), 5.10 (1H, t, $J = 7.1$ Hz), 3.89 (3H, s), 2.40–2.31 (1H, m), 2.06–1.99 (2H, m), 1.62 (3H, s), 1.58 (3H, s), 1.45–1.37 (2H, m), 1.10 (3H, d, $J = 6.7$ Hz); IR (neat) 3406, 2955, 1667, 1618, 1499, 1439, 1341, 1273, 1204, 1150, 984, 791 cm^{-1}.
14. *Spectral data for compound* **8**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.56 (1H, s), 7.59 (1H, d, $J = 8.9$ Hz), 6.29 (1H, d, $J = 8.9$ Hz), 3.86 (3H, s), 3.18 (1H, br d, $J = 12.8$ Hz), 2.52–2.44 (1H, m), 1.86–1.80 (2H, m), 1.67–1.52 (3H, m), 1.46–1.40 (1H, m), 1.37 (3H, s), 1.14–1.10 (1H, m), 1.05 (3H, s), 0.93 (3H, d, $J = 6.6$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.2, 162.5, 160.2, 128.6, 112.9, 109.6, 104.3, 78.3, 51.8, 48.8, 38.2, 35.4, 35.2, 32.7, 27.9, 27.5, 22.5, 19.1; IR (neat) 2949, 1663, 1622, 1582, 1489, 1439, 1339, 1260, 1209, 1138, 1086, 1069, 1003, 914, 883 cm^{-1}.
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16. *Spectral data for compound* **22**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.36–8.32 (1H, m), 7.82–7.79 (1H, m), 7.51–7.46 (2H, m), 7.43–7.39 (2H, m), 2.66–2.54 (2H, m), 1.94–1.90 (2H, m), 1.78–1.66 (1H, m), 1.61 (3H, s), 1.58–1.49 (1H, m), 1.29–1.11 (2H, m), 1.08 (3H, d, $J = 6.6$ Hz) 1.00–0.96 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.8, 133.0, 127.2, 125.5, 124.8, 124.1, 122.0, 121.9, 118.7, 118.4, 77.6, 47.1, 39.7, 35.9, 34.8, 32.6, 28.0, 27.6, 22.6, 20.1; IR (neat) 3055, 2922, 1572, 1507, 1458, 1385, 1265, 1209, 1144, 1096, 1020, 939, 909, 847, 745 cm^{-1}.
17. *Spectral data for compound* **24**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.93 (1H, d, $J = 8.4$ Hz), 7.83 (1H, d, $J = 8.0$ Hz), 7.67 (1H, d, $J = 8.9$ Hz), 7.53 (1H, dt, $J = 8.4$, 1.4 Hz), 7.38 (1H, dt, $J = 8.0$, 1.1 Hz), 7.14 (1H, d, $J = 8.9$ Hz), 2.95–2.80 (1H, m), 2.07–1.95 (2H, m), 1.75–1.67 (1H, m), 1.55 (3H, s), 1.44–1.20 (3H, m), 1.16 (3H, s), 1.05 (3H, d, $J = 6.5$ Hz), 1.00–0.88 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.5, 132.4, 129.7, 128.8, 128.0, 125.2, 124.2, 122.6, 120.0, 117.4, 77.6, 51.2, 42.5, 36.7, 36.0, 33.3, 28.4, 27.6, 22.6, 18.4; IR (neat) 3059, 2926, 1620, 1599, 1512, 1460, 1386, 1240, 1213, 1144, 1001, 981, 956, 908, 814, 748 cm^{-1}.
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22. The reported specific rotation values of compound **3** are $[\alpha]_D$ −93.6 (*c* 0.7, $CHCl_3$),[18] $[\alpha]_D$ −73.9 (*c* 0.014),[19] and $[\alpha]_D$ −74.1 (*c* 1, $CHCl_3$),[20] whereas those of compound **4** are $[\alpha]_D$ +82.9 (*c* 0.024)[19] and $[\alpha]_D$ +79.5 (*c* 1, $CHCl_3$).[20]