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Enantioselective Total Synthesis of Cannabinoids via a Tandem Conjugate Addition/Enolate Alkylation Annulation with Ambiphilic Organoboronates

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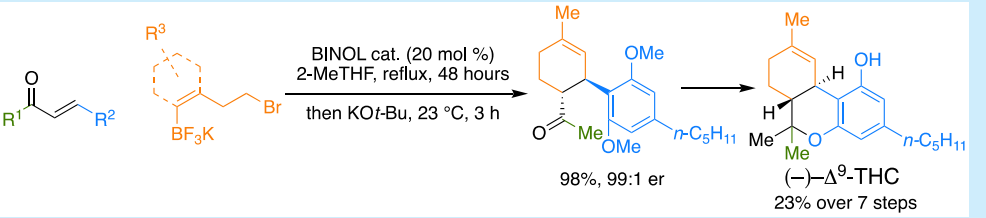

ABSTRACT: Cannabinoid research depends on synthesizing derivatives for structure−activity relationship studies. (−)-Δ^9-Tetrahydrocannabinol and cannabidiol were synthesized via a tandem enantioselective conjugate addition/enolate alkylation annulation with a novel ambiphilic trifluoroborate in seven steps. A new class of alkenyl and aryl ambiphilic trifluoroborates were synthesized and showed great compatibility with various functional groups, high yields, and excellent enantio- and diastereoselectivity. A novel benzo-fused cannabinoid analogue and tandem quaternary stereocenter-containing reaction products were synthesized with good to excellent enantioselectivity.

Since the discovery of (−)-Δ^9-tetrahydrocannabinol (THC) in 1964 [**1** (Figure 1)],[1] chemists have been attracted to its fascinating structure and biological activity. The binding of cannabinoids like THC and cannabidiol (CBD, **2**) to cannabinoid receptors CB1 and CB2 provides most of their pharmacological effects.[2] Many analogues, including those containing heterocycles (see **3** and **4**), have been synthesized for structure−activity relationship (SAR) studies to probe receptor binding interactions.[3,4] Importantly, the stereochemistry in THC and various analogues was found to directly impact receptor binding affinities,[5] which highlights a need for general strategies that control stereoselectivity when synthesizing natural and synthetic cannabinoids.[6] Therefore, cyclohexene ring A, which contains the two adjacent stereocenters in THC, is a highly intriguing site of modification for both synthetic and biological reasons. Herein, we report a concise high-yield enantioselective and diastereoselective synthesis of THC and CBD that enables cyclohexene modification via a novel organocatalyzed ambiphilic annulation using a haloalkylated alkenylboronate.

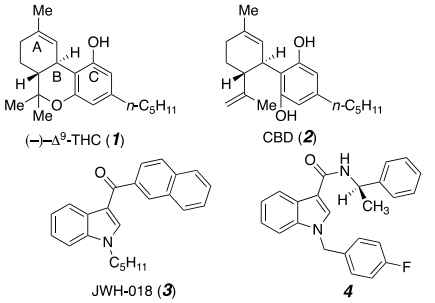

Figure 1. Selected natural and synthetic cannabinoids.

Although the cyclohexene ring of THC and CBD can be installed as a unit via a chiral pool strategy,[7,8] more modifiable enantioselective ring-forming approaches have been investigated (Figure 2). In 1997, Evans reported the first catalytic enantioselective route to THC via a bis(oxazoline)Cu(II)-catalyzed Diels−Alder reaction.[9] Trost utilized a molybdenum-catalyzed asymmetric alkylation in 2006.[10] In 2013, Zhou leveraged asymmetric hydrogenation,[11] and shortly thereafter, Carreira synthesized all four stereoisomers of THC via an elegant stereodivergent dual catalysis strategy.[12] Recently, in 2018 and 2019, Leahy[13] and Lupton[14] reported enantioselective total syntheses using an Ireland−Claisen rearrangement and asymmetric NHC catalysis, respectively.

Many of these synthetic approaches to THC require transition metal catalysis for stereocontrol, which can limit

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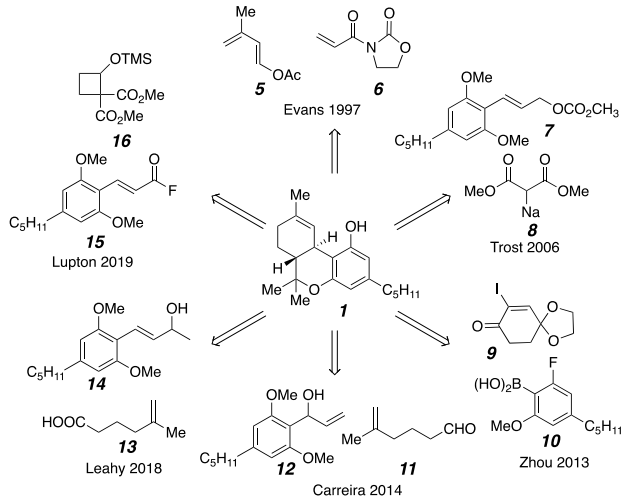


Figure 2. Catalytic enantioselective syntheses of Δ^9-THC.

analogue synthesis due to a lack of compatibility with heterocycles, halides, and other sensitive groups.[15,16] Additionally, for routes that require alkene metathesis to form the cyclohexene ring, analogues containing a fused aryl/heteroaryl ring in place of the double bond cannot be made [cf. **53** (vide infra)]. Consequently, a metal-free method that could allow modification of the cyclohexene would be highly beneficial to SAR studies. We hypothesized that an organocatalyzed tandem annulation reaction would provide that enantioselective method for synthesizing the cannabinoid core with maximum flexibility.

Several groups have developed enantioselective organocatalyzed reactions utilizing organoboron nucleophiles and BINOL-derived catalysts.[17−20] In particular, our metal-free conjugate addition method synthesizes β-stereocenters with excellent enantioselectivity and outstanding compatibility with heterocycles (Figure 3).[21] Alkenyl borates like **18** are activated by fluoride loss and binding first to chiral BINOL-derived

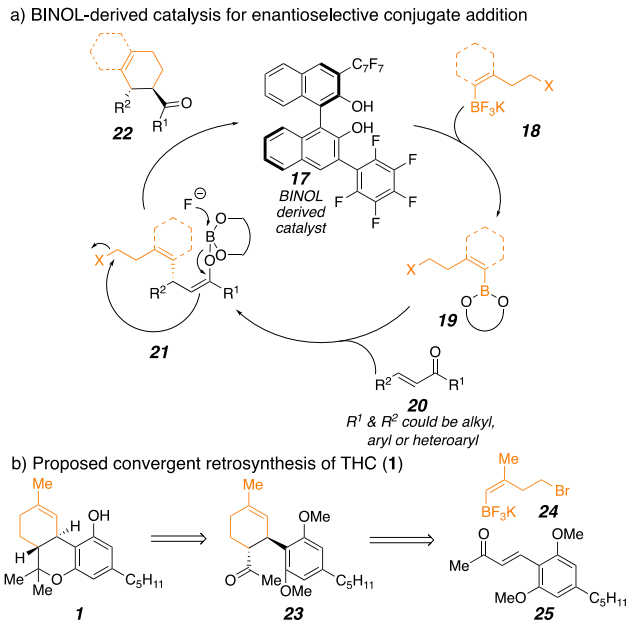
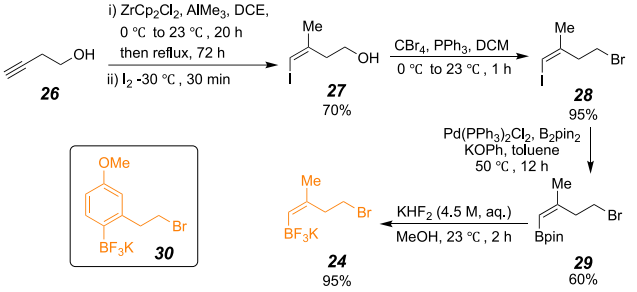


Figure 3. (a) Proposed conjugate addition/enolate alkylation annulation and (b) retrosynthetic analysis of THC.

catalyst **17** and then to the carbonyl of enone **20**.[20] Given that the nucleophile is inactive until that binding event, we believed that an electrophilic functionality could also be incorporated to provide a novel bench- and air-stable ambiphilic reagent **18** that would react intramolecularly with the intermediate enolate. Such a stable arrangement is improbable with traditional nucleophiles such as Grignard or organolithium reagents and is typically seen in only bench-stable reagents for ylides; ambiphilic reactivity is otherwise available only in transient reaction intermediates, such as in the trimethylene methane[22] or Piers annulations.[23] The powerful proposed annulation would provide rapid access to the cycloalkenyl rings in THC and its derivatives (Figure 3b), including those containing heterocyclic bioisosteres.

The synthesis of the postulated ambiphilic reagent commenced with alkynyl methylation[24] to generate *Z*-alkenyl iodoalcohol **27** in 70% yield (Scheme 1). A bromide leaving

Scheme 1. Synthesis of Ambiphilic Trifluoroborates



group was then incorporated via Appel reaction in 95% yield. Fortuitously, the planned Miyaura borylation synthesized the alkenyl boronate **29** in 60% yield without anticipated complications from oxidative insertion into the alkyl bromide of **28** or **29**. Treatment with aqueous KHF_2 provided ambiphilic alkenyl trifluoroborate **24** in 95% yield. Ambiphilic aryl trifluoroborate **30** was also synthesized through a similar approach.[25]

With the bench-stable ambiphilic reagents in hand, the total synthesis of THC began with the conjugate addition of alkenyl borate **24**, which was tested in several commonly used solvents for BINOL-catalyzed reactions.[25] Toluene and 1,2-dichloroethane provided efficient reactions[20] and showed full compatibility with the alkyl halide (Table 1, entries 1 and 2, respectively). For reasons explained below, a new reaction solvent for these transformations,[21] 2-MeTHF, was the only solvent that eventually allowed the complete annulation to occur in a single reaction. The stoichiometry and concentration were modified to decrease the amount of the nucleophile to only 1.2 equiv with 1 mmol of **25** at a concentration of 1 M while maintaining an excellent yield and enantioselectivity (entry 5).

Various enones were tested to show that these ambiphilic trifluoroborates would enable cannabinoid analogue development. It was confirmed during this study that the transient boron enolate (see **21** in Figure 3) was not sufficiently nucleophilic to react with the pendant alkyl halide. Additives like HMPA and DMPU were included to activate the enolate by Lewis base coordination to boron but failed to initiate the enolate alkylation to effect annulation.[25] Nevertheless, the conjugate addition worked very well with phenyl and alkyl substituents (Figure 4, **32** and **33**). Changing the enone

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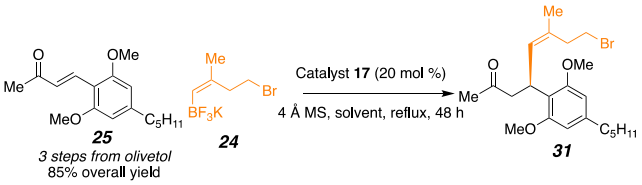
Table 1. Conjugate Addition Optimization



entry	solvent	concn (M)	yield (%) (er[a])
1	toluene	0.05	62[b] (99:1)
2	$ClCH_2CH_2Cl$	0.05	96[b] (99:1)
3	2-MeTHF	0.05	98[c] (99:1)
4[d]	2-MeTHF	0.8	98[c] (99:1)
5[e]	2-MeTHF	1	98[c] (99:1)

[a]er determined by HPLC with a chiral stationary phase. [b]Yields determined by integrating ^{1}H NMR peaks relative to 1 equiv of methyl(4-nitrophenyl) carboxylate as an internal standard. Three equivalents of **24** used. [c]Isolated yields averaged from two trials. [d]With 2 equiv of **24**. [e]With 1.2 equiv of **24**.

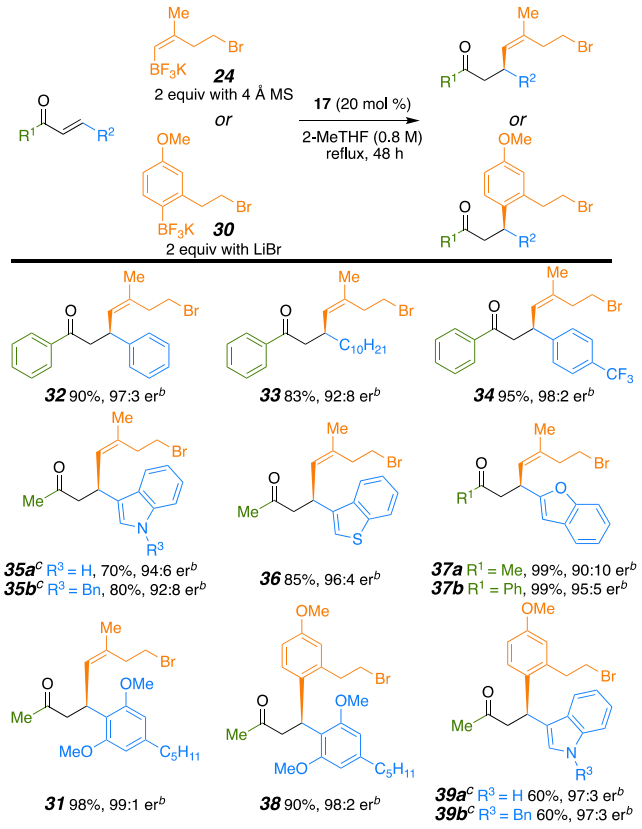


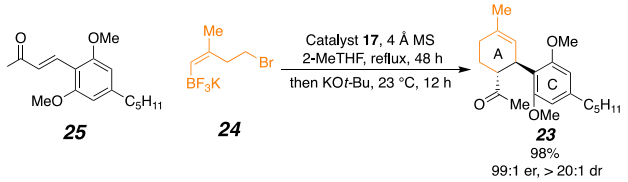
Figure 4. Conjugate addition scope. All yields are averages of at least two trials. [b]er was determined by HPLC with a chiral stationary phase. [c]Reactions completed in 2 h at the given concentration. See the Supporting Information for details.

electronics with an electron-withdrawing group on the β-aryl ring to produce ketone **34** did not cause deviation from a high yield and enantioselectivity. The conjugate addition also showed great tolerance with heteroaryl-substituted enones (**35**–**37**). Both unprotected and benzyl-protected indolyl enones had fast reaction rates, with similar yields and er's (**35a** and **35b**), which demonstrates that heteroaryls will be tolerated for analogue synthesis. Aryl trifluoroborate **30** also exhibited excellent performance in the conjugate addition. Product **38**, which has a structure similar to that of THC precursor **31**, was successfully obtained in 90% yield and 98:2 er. The aryl nucleophile also showed promising compatibility with electrophiles containing heteroaryl substituents (**39a** and **39b**).

The isolation of ketones **32**–**39** showed that additional base would be needed for enolate alkylation. Although 1,2-dichloroethane gave an almost quantitative yield for conjugate addition (Table 1, entry 2), it did not allow the alkylation to occur with any of the bases examined.[25] This failure required the consideration of other solvents that could allow alkylation. To assess potential conditions for alkylation, isolated product **31** was dissolved in THF, and several bases were examined (Table 2, entries 1–4). Potassium *tert*-butoxide was the most effective of those considered, as it gave both a high yield and excellent diastereoselectivity (entry 4). We were then eager to combine the conjugate addition and alkylation into a single reaction.[26] An ideal solvent would replicate the polar aprotic properties of THF for the enolate alkylation annulation while having the noncoordinating nature and increased boiling point of 1,2-dichloroethane or toluene to ensure a good performance in the conjugate addition.[27] 2-MeTHF, an ecologically friendly solvent,[28,29] was found to be the perfect bridge between these two solvent characteristics. It not only proved to be excellent for the enolate alkylation annulation (Table 2, entry 5) but also provided high yield and enantioselectivity in the conjugate addition (Table 1, entries 3–5).

Satisfyingly, the new solvent produced amazing results for the combined tandem reaction (Scheme 2). Key THC

Scheme 2. Ambiphilic Annulation for the THC A-Ring



intermediate **23** was obtained using enone **25** in five steps from alcohol **26** as a single diastereomer in almost quantitative yield (98%) with outstanding er (99:1).[30] Modification of enone and trifluoroborate precursors could provide access to

Table 2. Enolate Alkylation Optimization

entry	base (equiv)	solvent	temp (°C)	time (h)	result[a]
1	LiHMDS (1.1)	THF	−78 to 23	2	0%
2	LDA (0.9)	THF	−78 to 23	10	0%
3	KHMDS (0.9)	THF	23	8	0%
4	KO*t*-Bu (3.0)	THF	23	12	98%, 99:1 er,[b] >20:1 dr
5	KO*t*-Bu (3.0)	2-MeTHF	23	12	98%, 99:1 er,[b] >20:1 dr

[a]Isolated yields. [b]er determined by HPLC with the chiral stationary phase.

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analogues with different A ring sizes and/or different ring C aryl or heteroaryl groups, each bearing various substituents.

The tandem conjugate addition/enolate alkylation annulation conditions were applied to the same array presented in Figure 4, resulting in high stereoselectivity and compatibility with various functional groups (Figure 5). For the alkyl, aryl,

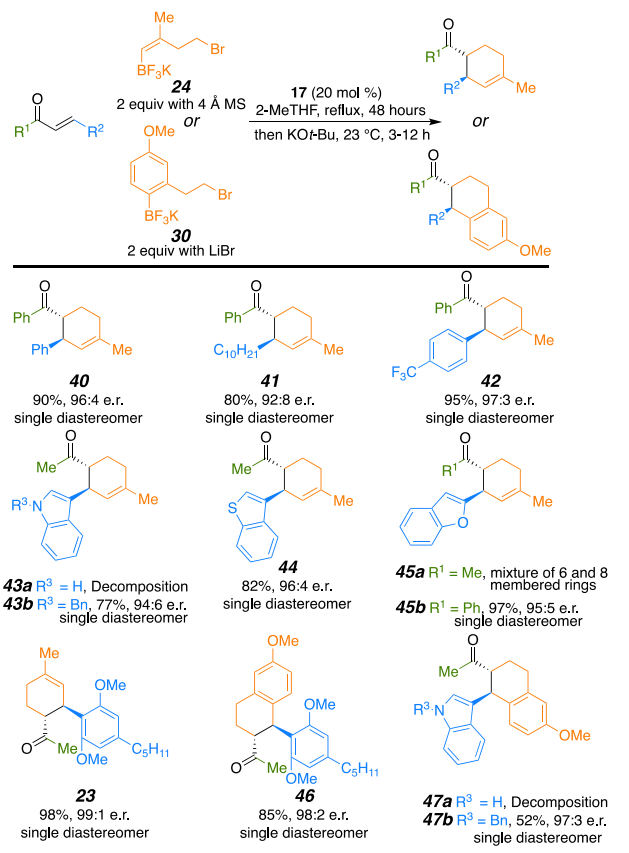
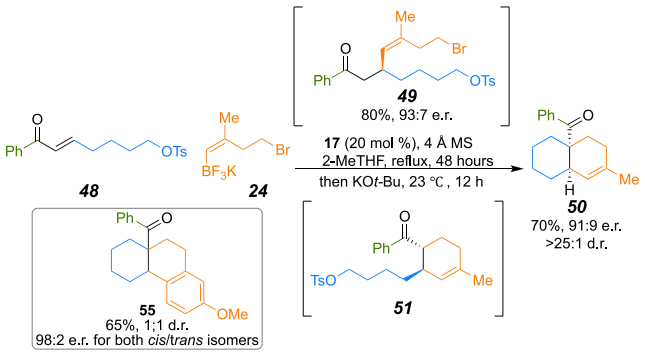


Figure 5. Conjugate addition/enolate alkylation annulation. All yields are averages of at least two trials. er was determined by HPLC with a chiral stationary phase. dr was determined by crude ^{1}H NMR. Reaction times differ due to the sensitivity of different substrates under basic conditions (see the Supporting Information for details).

and electron-poor aryl substrates, the tandem yield and enantioselectivity did not deviate from those obtained in the isolated conjugate addition, even though an additional transformation was incorporated (**40**–**42**). Consequently, the efficiency of this annulation is greatly enhanced in the combined, single-reaction approach. On the contrary, two of the heteroaryl substrates provided additional challenges for the alkylation stage of the annulation. The use of unprotected indolyl and benzofuranyl substrates gave a complex mixture after treatment with a base (see **43a**, **45a**, and **47a**). For indolyl substrates, this problem was easily addressed by using a protecting group to prevent deprotonation at the indole NH, and both products **43b** and **47b** were obtained successfully with good yield and er. Notably, product **43b** resembles recently developed synthetic cannabinoids like indoloketone **3** and chiral indoloamide **4**, but it has the THC cyclohexenyl ring incorporated in high enantiopurity. In the case of the benzofuranyl substrate, some formation of an eight-membered ring product was observed, presumably due to enolate formation on the methyl side of the ketone.[25] Indeed, a phenyl ketone derivative prevented the competing enolate formation, and **45b** was obtained in 97% yield and 94:6 er as a single diastereomer. The benzothiophene substrate also gave a high yield and enantioselectivity for the tandem reaction (see **44**). A precursor for a THC analogue, **46**, that would be inaccessible by prior enantioselective catalysis routes was obtained in 85% yield and 98:2 er.

Given that the addition of excess KO*t*-Bu could enable additional enolate formation, subsequent alkylation could occur to furnish polycyclic products containing all-carbon quaternary centers from an enone like **48** with a pendent alkyl halide or tosylate (Scheme 3). Again, the success of this

Scheme 3. Double Alkylation to Form a *cis*-Decalin with a Quaternary Carbon Stereocenter



strategy depended on the compatibility of nucleophilic organoborates to traditional electrophiles. Conjugate addition in isolation gave β-branched **49** in 80% yield and 92:8 er. In the tandem conjugate addition/enolate alkylation, *cis*-decalin **50** was obtained in 70% yield and 90:10 er with an outstanding dr that was higher than 25:1. The initial stereocenter set by conjugate addition effectively controlled the subsequent alkylations. Apparently, the enolate derived from **49** reacts faster with the alkyl bromide than the alkyl tosylate, because the resulting intermediate **51** could be isolated in small quantities and identified via ^{1}H NMR. Surprisingly, the diastereoselectivity was different for aryl ambiphile **30**, which gave the corresponding fused tricycle **52** in 65% yield. While the product was obtained as a 1:1 mixture of diastereomers, each was produced in >98:2 er.[25]

After exploring the promising potential of these ambiphilic boronates, we returned to complete the total syntheses of THC and CBD. The former was successfully obtained in 62% yield after treatment of **23** with methyl magnesium iodide and $ZnBr_2$ (Scheme 4).[12,13] CBD was synthesized from **23** by deprotection of the methoxy groups after a Wittig olefination.[13] All spectral data for both compounds were identical to those previously published.[7−14] This approach was also suitable for synthesizing a novel THC analogue **53** from benzannulated **46**, and we anticipate many additional analogues will be synthesized via this strategy, as well as other cannabinoids such as (−)-cannabidiolic acid.[31]

The total synthesis of THC was accomplished in high efficiency via a novel conjugate addition/enolate alkylation annulation reaction enabled by sophisticated ambiphilic organoborate alkyl halides, which enantioselectively set two adjacent ring stereocenters in a single reaction. These ambiphilic boronates are readily synthesized and bench stable. By simple modification of trifluoroborate ambiphiles, analogues can be obtained that were inaccessible with prior

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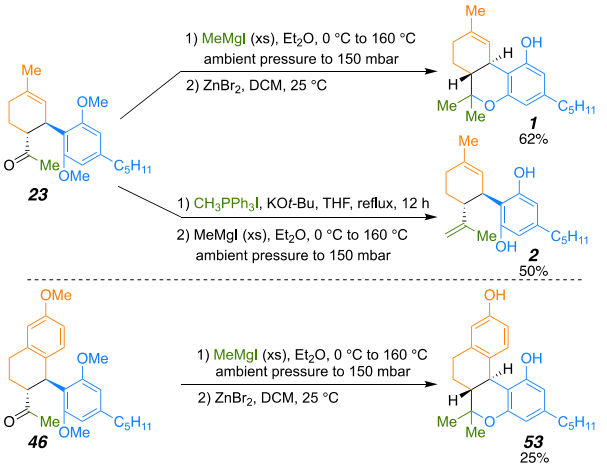
Scheme 4. Synthesis of THC, CBD, and A Benzannulated Analogue



enantioselective catalytic routes. All-carbon quaternary centers can even be generated with high enantioselectivity through enone modification. This metal-free method shows high compatibility with various functional groups, including heteroaryl substituents, and its modularity will allow access to novel cannabinoid analogues, such as those with cyclopentene and/or benzo-fused A-rings. Work to systematically synthesize a library of such analogues is now underway.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c00090.

Experimental procedures, reaction optimization, and spectral data (PDF)

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Author Contributions

J.A.M. and J.L. conceptualized the research and wrote the manuscript. J.L. performed investigations. J.A.M. supervised the project.

Notes

The authors declare no competing financial interest.

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