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Review article

Stereoisomers of cannabidiols and their pharmacological activities – A potentially novel direction for cannabinoids

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ABSTRACT

Cannabidiol (CBD), a bicyclic non-psychoactive cannabinoid biosynthesized by *Cannabis* spp. of plants, has attracted significant interest in the past decade due to its therapeutic properties. In 2018, the US FDA approved Epidiolex®, a CBD-based drug for the treatment of two rare epileptic seizure disorders.

CBD possesses two chiral centers at C3 and C4 on its terpenoid moiety and exhibits *cis–trans* stereoisomerism along the C3–C4 bond axis. (−)-*trans*-(3*R*,4*R*)-CBD, the natural CBD, is biosynthesized by the cannabis plant, while the unnatural (+)-*trans*-(3*S*,4*S*)-CBD is obtained *via* chemical synthesis. Both *trans* isomers exhibit broad *in vitro* and *in vivo* biological activities; typically, the unnatural stereoisomer (+)-*trans*-CBD and its derivatives exhibited more potent activities in comparison to the corresponding (−)-*trans* isomers. On the other hand, *cis*-CBD isomers have only been reported recently and can undergo epimerization into *trans* isomers.

There is a significant opportunity to explore unique synthetic methods and biological activities of stereoisomers of CBD that may pave the path for the development of novel therapeutics. Herein, as a novel direction in cannabinoids, we review the chemistry of CBD stereoisomers, their structure–activity relationships, target selectivity and efficacy in animal models.

1. Introduction

Cannabinoids, biosynthesized by *Cannabis* spp. of plants, interact with multiple drug targets with a range of affinities, where they function as full or partial agonists, antagonists or even inverse agonists.[1] Such targets include including 5-hydroxytryptamine receptor 1A (5-HT1A), adenosine A1 and A2A receptors, dopamine (D2) receptors, peroxisome proliferator-activated receptor gamma (PPARγ), fatty acid amide hydrolase (FAAH), transient receptor potential vanilloid channels 1–5 (TRPV1-5), transient receptor potential ankyrin channel 1 (TRPA1), transient receptor potential melastatin channel 8 (TRPM8), as well as sodium ($Na_V1.7$) and calcium channels, G protein-coupled receptors 55 and 12 (GPR55 and GPR12, respectively) and cannabinoid receptors types 1 and 2 (CB_1R and CB_2R, respectively).[2–7]

CB_1R is localized mainly in the central nervous system (CNS), while CB_2R is characterized as a peripheral receptor for cannabinoids.[8–11] CB_1R and CB_2R serve as binding sites for endogenous and exogenous ligands, as well as enzymes synthesizing and degrading those ligands.[12] CB_1R is involved in biological pathways involving appetite regulation[13–15] pain sensitivity[13,16,17], mood and memory[13,18–20], neurogenesis,[13,18] neurotransmission[13] and psychotropic effects.[13] In addition to pain modulation and neurogenesis, CB_2R is also involved in immune responses[9,13,15] and more importantly, is not associated with the unwanted psychotropic effects.[13,18]

Cannabidiol ((−)-CBD, **1**, referred to as CBD) is a popular bicyclic cannabinoid that has gained significant interest in the recent years (Fig. 1). CBD has demonstrated anti-inflammatory activities in T cell-mediated animal models of collagen-induced arthritis, autoimmune diabetes, and autoimmune hepatitis.[21–23] The T cell-based immunoregulatory activities of CBD are due to the downregulation of the transcription of various proinflammatory genes that control the Th17 function of encephalitogenic T cells.[24–26] CBD treatment was also shown to activate the interferon (IFN)-dependent anti-proliferative genes and potentiate the expression of genes downregulating T cells

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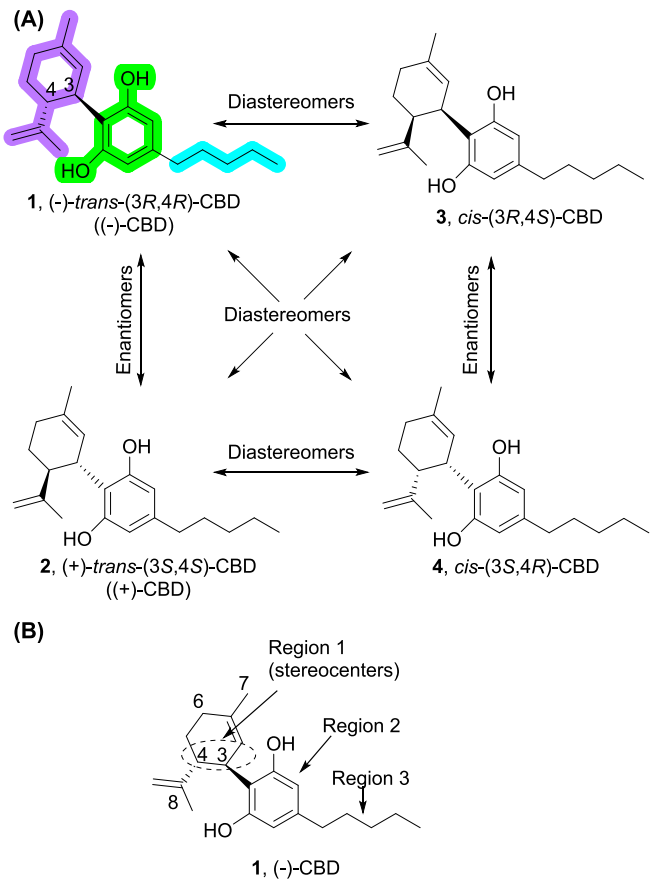


Fig. 1. (A) Chemical structures of the four CBD stereoisomers. The structural components of CBD (**1**) are highlighted as follows: terpenoid ring is purple, the resorcinol group is green and the *n*-pentyl chain is cyan. *Trans* isomers are compounds **1** and **2**, and *cis* isomers are **3** and **4**. (B) Pharmacophore regions in CBD (**1**).

communication and antigen presentation.[24] In addition to increasing phagocytosis of the BV2 (microglial cell line) cells, CBD also induced the expression of TRPV1 and TRPV2 receptors.[27] (see Fig. 2).

CBD also ameliorated clinical symptoms in a mouse model of experimental autoimmune encephalomyelitis (EAE) induced by oligodendrocyte glycoprotein 35–55 (MOG_{35-55}).[28–31] As a potential treatment option for multiple sclerosis (MS), an autoimmune disorder with a progressive neurodegenerative component, CBD was shown to be as effective as Copaxone® in improving clinical symptoms in an EAE mouse model.[32] In these mice, CBD treatment also reduced inflammatory insult on the CNS, including T cell infiltration, microglial activation, and axonal damage.[33–36]

CBD also exhibits biological activity at multiple receptors. CBD shows weak affinity for CB_1R and CB_2R and lacks the associated CB_1R-mediated psychoactivity; however, its effects on various cells and in various animal models are quite diverse.[37] CBD and its derivatives show therapeutic activities as anti-neurodegenerative, neuroprotective, anti-inflammatory and anti-proliferative agents by regulating CB_1R and CB_2R activities.[38] (−)-CBD reduces the potency and efficacy of the endogenous ligand 2-arachidonoylglycerol (2-AG) and exogenous Δ^9-tetrahydrocannabinol (Δ^9-THC) at CB_1R, by acting as a negative allosteric modulator (NAM) of CB_1R at concentrations lower than the predicted affinity of CBD for the orthosteric site of CB_1R.[39] Similarly, it is also a NAM of the binding and functional effects of agonists in CB2R-mediated signalling.[40] CB_1R and CB_2R are thus important therapeutic targets and compounds that selectively bind to one of these receptors offer a more targeted approach for treatment.

In the past decade, CBD has attracted significant interest due to its clinical efficacy as an immunomodulatory, anti-inflammatory and anti-epileptic agent.[41] CBD was evaluated in several clinical trials involving patients with MS, epilepsy, cancer, Rett syndrome (RTT), Tourette syndrome (TS), Post-Traumatic Stress Disorder (PTSD), sleep and anxiety disorders, with mixed results.[38] CBD is considered relatively safe when used at recommended doses for subchronic treatment of various health conditions.[42–44] However, there is the potential for adverse effects and drug-drug interactions mostly due to its interactions with CYP450 enzymes and various efflux transporters.[45]

A CBD formulation, Epidiolex®, was approved by the United States Food and Drug Administration (US FDA) in 2018, for the treatment of two rare childhood epileptic seizure disorders, Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS).[46–48] In 2020, CBD was approved for the treatment of tuberous sclerosis complex (TSC) associated seizures.[49] CBD is also used clinically in combination with other cannabinoids. For example, Sativex®, a cannabis extract of equal amounts of CBD and Δ9-THC, was approved for the treatment of MS-associated pain and spasticity.[48] Overall, there is great optimism in the scientific and clinical communities about CBD and its potential as a therapeutic agent.

While pharmacological research with CBD is likely to continue due to easier access, there is still much to be explored about the chemistry and biology of CBD analogs.[50–52] One of the most underexplored areas of research involves the stereoisomers of CBD and their biological activities, with only a handful of reports examining the enantioselective synthesis of CBD and its derivatives. This review will highlight various chemical and biological activity profiles of CBD stereoisomers, their derivatives, and exciting opportunities in this area.

2. Chemical structure of CBD

CBD contains a terpenoid ring connected to a resorcinol moiety linked to an *n*-pentyl hydrocarbon tail (Fig. 1A). Due to the two chiral centers on the terpenoid moiety, CBD shows *cis–trans* stereoisomerism along the C3–C4 bond (terpenoid numbering system), resulting in four possible diastereomers.[53,54] Since its discovery in 1940, various strategies for the total synthesis of CBD have been pursued, including a few stereoselective routes.[55–58] As illustrated in Fig. 1B, there are three primary regions in CBD, which serve as pharmacophores that may be modified for enhanced therapeutic effects.

3. Synthesis of CBD and its stereoisomers

CBD is a carbon-rich molecule and, starting materials such as olivetol (**6**) and phloroglucinol (**8**) have served well for various synthetic approaches (Scheme 1). Reported by Petrzilka et al. as early as in 1967, the Friedel–Crafts reaction of **6** was the first and most frequently used synthetic approach for the stereoselective synthesis of (−)-CBD (Scheme 1A, Fig. 2).[59,60] This approach involved using (+)-*cis*- or (+)-*trans*-*p*-mentha-2,8-dien-1-ol (**5a** or **5b**, respectively) in the presence of catalytic zinc chloride, oxalic acid, picric acid, maleic acid, or *N*,*N*-dimethylformamide dineopentyl acetal, resulting in low yields of (−)-CBD (*ca.* 28 %) due to poor regioselectivity. However, the absolute stereochemistry of (−)-CBD could be clearly defined based on the known stereochemistry of **5**.[60] Stronger acids such as *p*-toluene sulfonic acid, trifluoroacetic acid, and boron trifluoride-etherate ($BF_3{\cdot}OEt_2$) induced cyclization, leading to the thermodynamically stable, cyclized regioisomer Δ9-THC.[60] Various attempts to improve yields for this reaction included modifying reaction conditions, such as high pressure (7–8 kbar)[61] and using Lewis acids like $BF_3{\cdot}OEt_2$ on alumina,[57] silver triflimide,[62] and scandium triflate,[63] which gave 44–55 % yields (Scheme 1A). Chiurchiù et al. modified the Friedel–Crafts reaction by using a continuous-flow chemical synthesis for the reaction between **6** and acetyl isopiperitenol (**7**) to obtain CBD in 55 % yield, with increased regioselectivity (Scheme 1A), thus limiting the production of other regioisomers.[64] Here, the stereochemistry of CBD was pre-determined

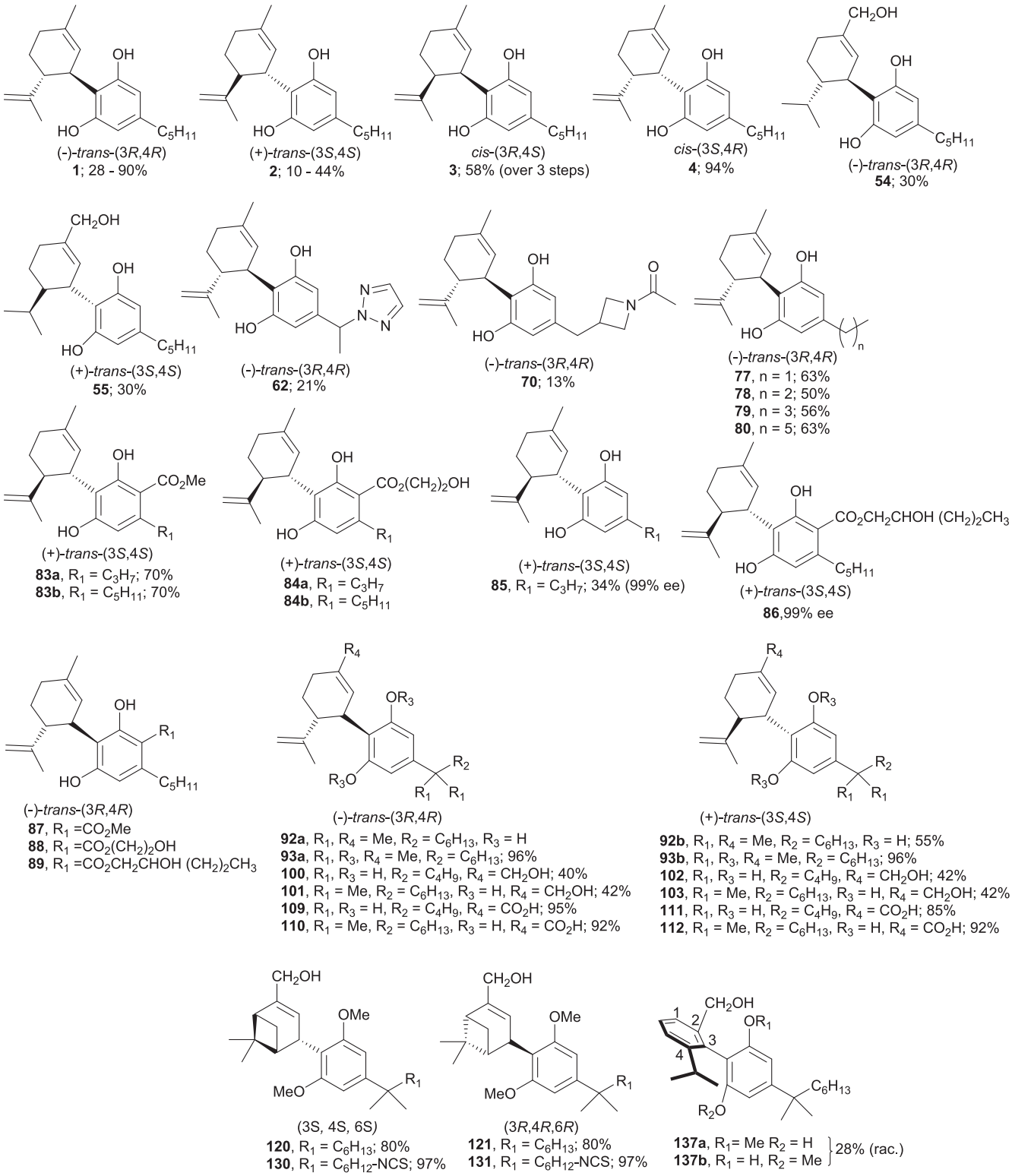
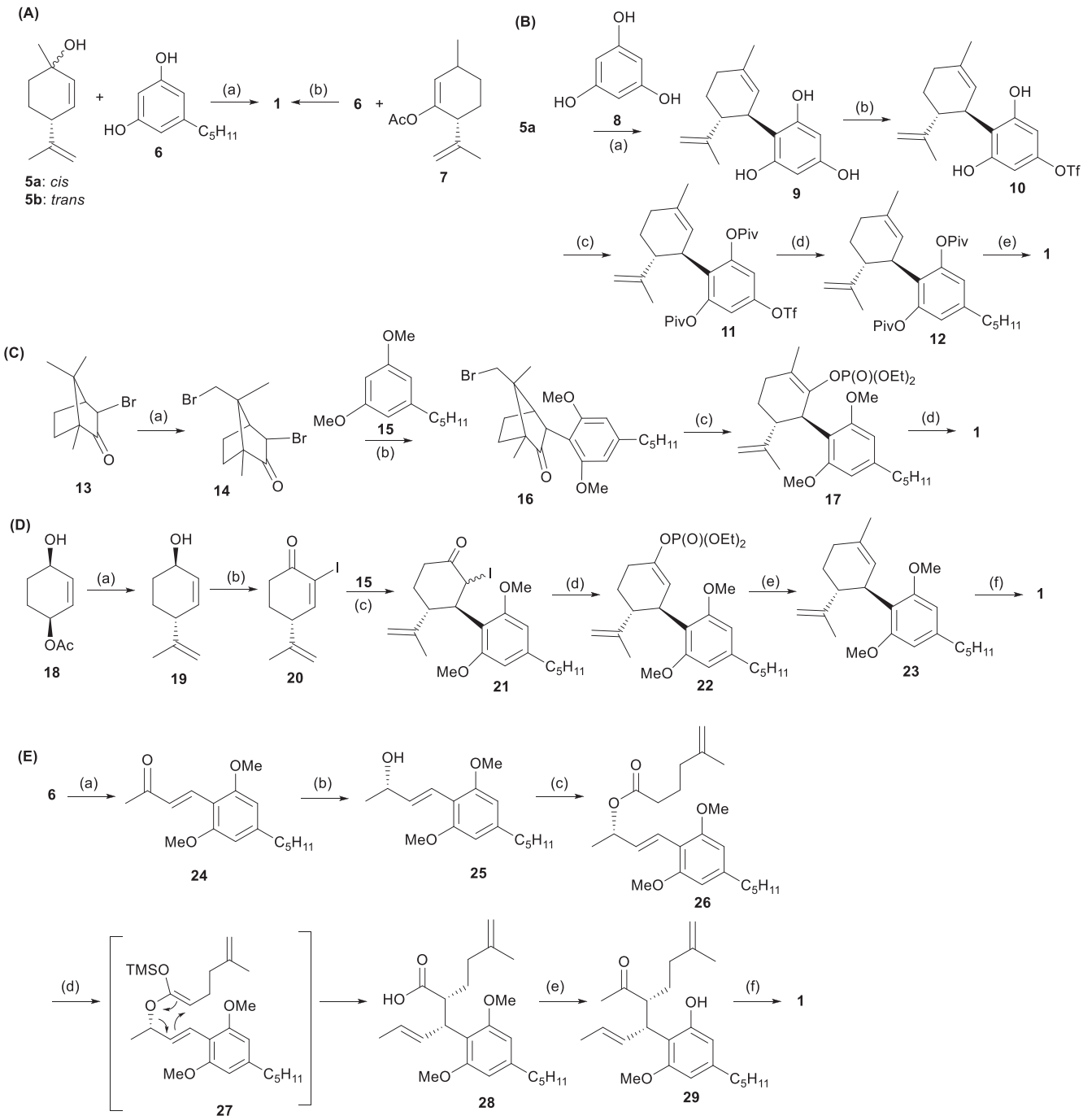


Fig. 2. Summary of the chemical structures and isolated yields of CBD stereoisomers and their analogs discussed herein.[55,57–72,74–81,83–86]

by that of **7**.

To prevent the formation of regioisomers, Gong et al. replaced olivetol (**6**) with phloroglucinol (**8**) for the electrophilic aromatic substitution reaction, thus obtaining **9** in higher yields (Scheme 1B).[58] The selective protection of the *p*-hydroxyl group with triflate, followed by pivaloylation gave **11**. Subsequent steps of Negishi coupling with *n*-pentyl zinc chloride and deprotection with methyl magnesium bromide provided (−)-CBD (**1**) in 52 % overall yield (Scheme 1B).

Vaillancourt and Albizati reported an elegant stereoselective total synthesis of CBD from camphor (Scheme 1C).[65] Monobromo camphor (**13**) was brominated to 3,9-dibromocamphor (**14**), followed by coupling with the cuprate of dimethoxyolivetol (**15**) to obtain the *endo* product **16** (Scheme 1C) exclusively. Conversion into its phosphoester derivative **17**, followed by reduction, gave CBD (Scheme 1C).



Scheme 1. Various methods for the stereoselective synthesis of (−)-CBD (1): (A) Friedel–Crafts reaction,[59,61–66] (B) Friedel–Crafts-Negishi coupling reaction,[60] (C) Nucleophilic substitution reaction,[67] (D) Nucleophilic Addition reaction,[68] and (E) Intramolecular Ireland-Claisen rearrangement.[69,70] Reagents: (A) (a) Acids or Lewis acids, 80 °C; (b) $BF_3{\cdot}OEt_2$, 7 min, rt; (B) (a) $BF_3{\cdot}OEt_2$, anhyd THF, 0 °C; (b) Tf_2O, 2,6-lutidine, DCM, 25 °C, 78 %; (c) Pivaloyl chloride, DMAP, DCM/pyridine, 12 h, 25 °C; (d) $C_5H_{11}ZnCl$, $Pd(dppf)Cl_2$, LiCl, anhyd THF, 60 °C, 90 %; (e) MeMgBr, toluene, 110 °C; (C) (a) HSO_3Cl, Br_2, 7 h, 10 °C, 63 %; (b) (i) ^{t}BuLi, anhyd THF, 3 h, −10 °C; (ii) CuI, anhyd THF, 20 mins, 0 °C, (iii) anhyd THF, DMSO, rt, 71 %; (c) Na-naphthalenide, $PO(OEt)_2Cl$, HMPA, −20 °C, 89 %; (d) $Li/MeNH_2$, ^{t}BuOH, anhyd THF, 1 h, −10 °C; (D) (a) (i) $CH_2=C(Me)MgBr$, $ZnCl_2$, TMEDA, THF, rt; (ii) $CH_2C(Me)MgBr$, $NiCl_2(tpp)_2$, THF, rt, 80 %; (b) (i) Jones reagent, acetone, rt; (ii) I_2, DBHQ, pyridine, rt, 76 %; (c) (i) *n*-BuLi, DME, Et_2O, rt; (ii) CuCN, Et_2O, −78 °C; (iii) $BF_3{\cdot}OEt_2$, Et_2O, −78 °C; (d) (i) EtMgBr, THF, 0 °C; (ii) $ClP(O)(OEt)_2Cl$, THF, 0 °C; (e) MeMgCl, $Ni(acac)_2$, THF, rt, 84 %; (f) MeMgI, 165 °C, 80 %; (E) (a) (i) Me_2SO_4, K_2CO_3, acetone, 80 °C; (ii) s-BuLi, TMEDA, DMF/THF, rt; (iii) NaOH, H_2O, acetone, 60 °C, 74 %; (b) (R)-2-Methyl-CBS-oxazaborolidine, $BH_3{\cdot}$THF, toluene, 30 min, −78 °C, 94 % (77 % ee); (c) (i) 5-methyl-5-hexenoic acid, DCC, DMAP, DCM, rt, 93 %; (d) (ii) KHMDS, toluene, 1 h, −78 °C; (iii) TMSCl, pyridine, rt, 77 % (94 % ee); (e) MeLi, Et_2O, rt, 72 %; (f) (i) Grubbs' 2nd gen., DCM, 40 °C; (ii) $MePh_3PBr$, ^{t}BuOK, THF, rt; (iii) MeMgI, Et_2O, 1.5 h, 160 °C, 150 mbar, 35 %.

Kobayashi et al. also reported a multi-step synthetic approach for CBD (Scheme 1D).[66] The key step in controlling the *trans*-geometry was the nucleophilic addition of a copper complex of dimethoxyolivetol (**15**) to the Michael acceptor **20** in the presence of $BF_3{\cdot}OEt_2$ to yield compound **21** (Scheme 1D). The ethylphosphonate ester **22** was methylated to **23**, and subsequently yielded CBD.

CBD has also been synthesized via the stereoselective cyclohexene ring (Scheme 1E).[67,68] In this method, diastereoselectivity was achieved

during the [3,3]-sigmatropic rearrangement of **26** (Ireland-Claisen rearrangement) by treatment with potassium hexamethyldisilazane and trimethylsilyl chloride resulting in **28** with the required stereochemistry, leading to the final enantiomer, (−)-CBD (**1**).

The synthetic route for the unnatural enantiomer (+)-CBD (**2**) was first reported by Cardillo et al. in 1972 (10 % yield) and later by Hanuš et al. in 2005 (Scheme 2A).[55,69] Olivetol (**6**) was added to (−)-*p*-mentha-1,8-diene-3-ol (**31**) using Friedel–Crafts conditions, yielding a non-stereoselective path. However, Golliher et al. adopted an asymmetric synthesis method to obtain (+)-CBD (**2**) from the key intermediate (1*S*,6*R*)-isopiperitenol (**31b**) in 22 % yield; this precursor was obtained in four steps from (+)-carvone (**32**) (Scheme 2B).[70] Grimm et al. recently accomplished the synthesis of *trans*-(1*S*,6*R*)-isopiperitenol (**31b**) via asymmetric cyclization of neral, and synthesized *trans*-(−)-CBD stereoselectively.72 Bosquez-Berger et al. also synthesized **2** using the Friedel–Crafts reaction of the chiral compound **35** with **6** (Scheme 2C).[72]

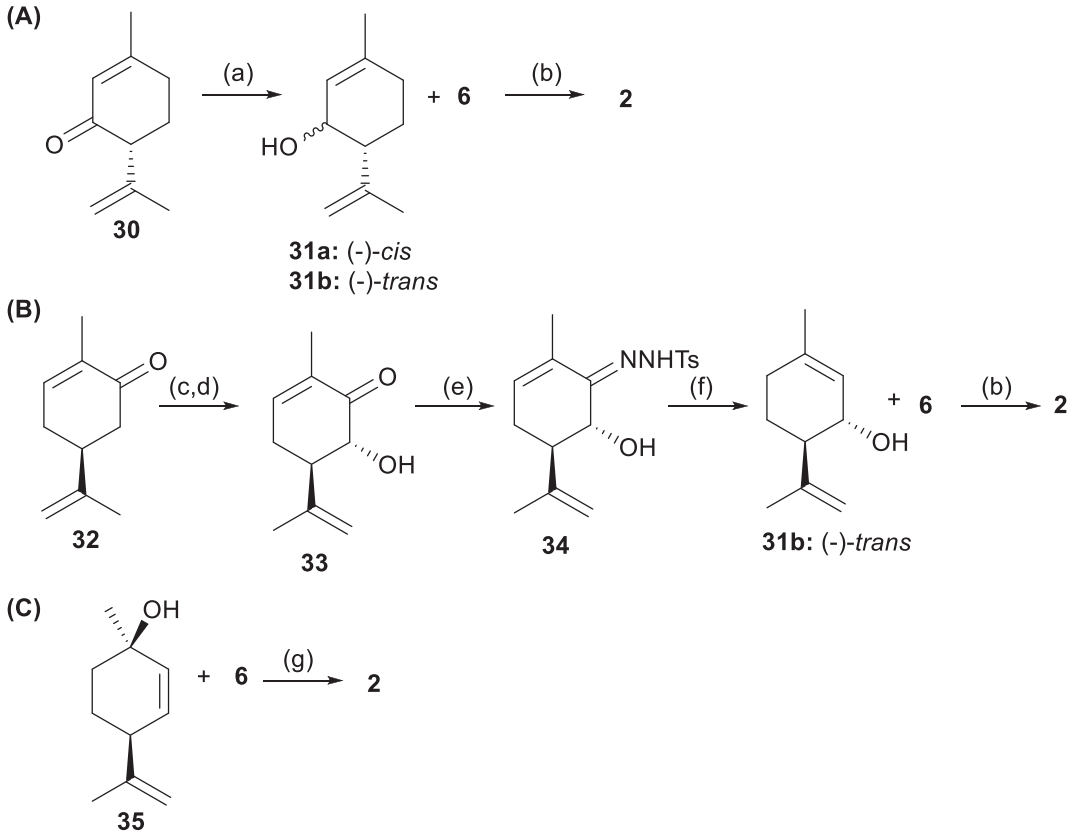
In 1977, Handrick et al. reported the first synthesis of *rac*-(±)-*cis*-CBD isomers, **3** and **4**.[73] Following the approach in Scheme 1B, Abdur-Rashid et al. later reported the synthesis of individual *cis* stereoisomers of CBD, **3** and **4**, as minor products (Schemes 3A and 3B).[74] When the *cis*-**5a** starting material was used in the initial step of the Friedel–Crafts reaction, they observed the formation of a major *trans* intermediate **36** (95 %), along with the minor *cis* intermediate **39** (5 %) and separated these isomers by chromatography (Scheme 3A). To obtain **1** and **4** in pure forms, the following processes were carried out on the corresponding intermediates **36** and **39**: regioselective hydroxyl group protection with triflate and trimethylsilyl groups, Negishi coupling of pentyl magnesium bromide, followed by deprotection. Likewise, the *trans*-isomer **5b** produced intermediates **40** and **41**, subsequently giving compounds **2** and **3** (Scheme 3B). It is noteworthy that the *cis* isomers were thermodynamically unstable, and reproducibility of these reactions was challenging due to epimerization to *trans* isomers.

More recently, the (−)-*cis*-CBD (**3**) was synthesized asymmetrically using an enantioselective Diels-Alder reaction (Scheme 3C).[75] Following protection of the hydroxyl groups of olivetol **6**, the ethoxyethyl diether **42** was subsequently converted to the diene **44**. Using acrolein, a prolinol-based catalyst (*R*-Cat$_8$) and a co-catalyst, the key Diels-Alder step was performed on **44** to selectively yield the enantiomer *endo*-*cis*-(*3R,4S*) **45a**, which was subjected to Pinnick oxidation and methylation to afford the *cis*-product **47a** in 59 % yield over three steps (99.5:0.5 *er*). Ester **47a** was converted to **3** in three steps (58 % yield), following preparative HPLC purification of a 9:1 *cis/trans* mixture.[75] The (−)-*trans*-CBD (**1**) was consequently obtained from a *cis/trans* mixture **45**, using two key changes: (i) epimerization of **45a,b** with sodium methoxide giving *trans*-(*3R,4R*) **45c** and (ii) esterification of the *trans*-(*3R,4R*) **45c** to **47b** by electrochemical oxidation (Scheme 3D). Likewise, (+)-*trans*-CBD (**2**) was subsequently synthesized following the Diels-Alder reaction of the diene dimethoxyolivetol analog of **44** with the *S*-Cat$_8$ prolinol catalyst, by incorporating the adaptations made for (−)-*trans*-CBD (**1**) (synthesis not shown).

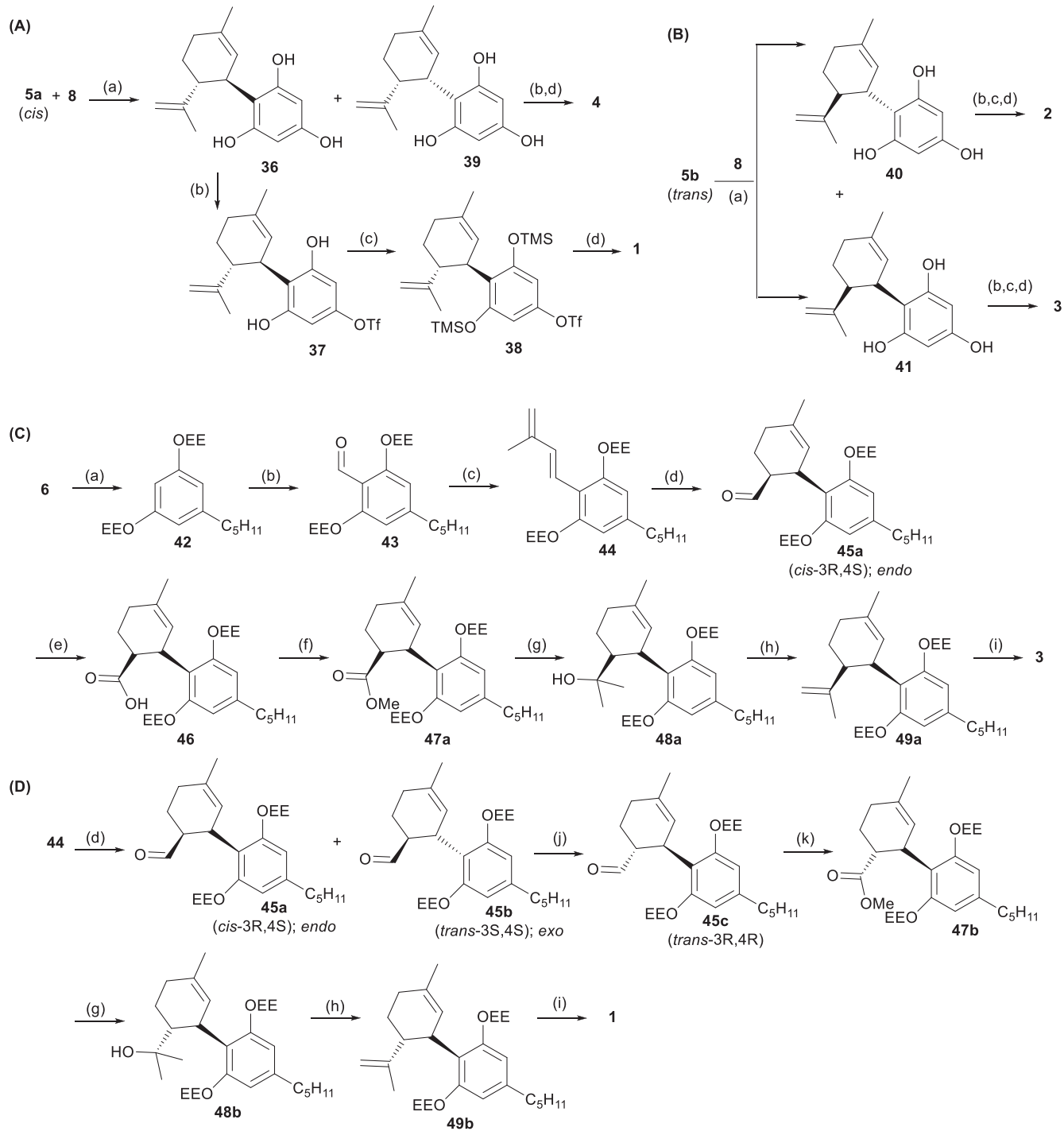
4. Synthesis of CBD analogs and their stereoisomers

Kozela et al. synthesized **54** (HU-446) and **55** (HU-465), which are 8,9-dihydro-7-hydroxy-CBD derivatives (Scheme 4, Fig. 2).[76] After reduction of (−)-CBD (**1**) followed by acylation, compound **52** was obtained and oxidized to yield a mixture of 7-hydroxy derivative **53** and its regioisomer. This mixture was carried forward without separation and reduced to obtain **54**. Under similar conditions starting with olivetol (**6**) and **50**, compound **55** was also obtained.

CBD derivatives with heterocyclic modifications on region 3 of the resorcinol ring represent an interesting group of compounds. For



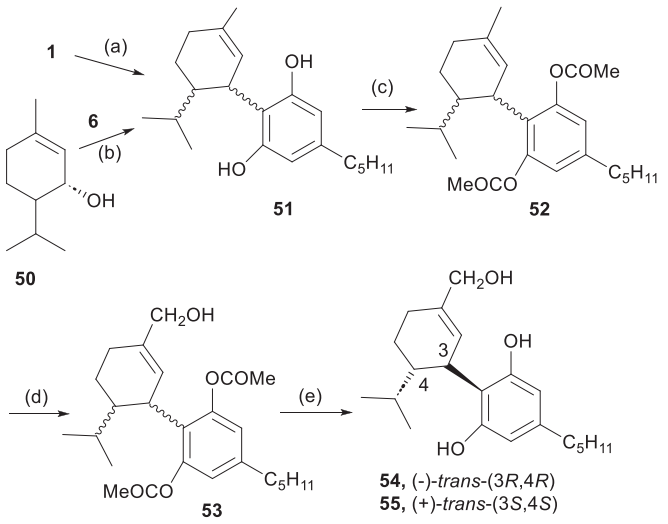
Scheme 2. Synthesis of (+)-CBD (2) via non-stereoselective (A)[57,71] and stereoselective methods (B[72,73] and C[74]). Reagents: (a) $NaBH_4$ (b) $BF_3.OEt_2$, basic Al_2O_3, anhyd. DCM, 40 °C, 44 %; (c) (i) LDA, TMSCl, anhyd THF, 2 h, −80 to 0 °C; (d) (i) m-CPBA, DCM, 1.5 h, 0 °C; (iii) HCl, MeOH, 58 %; (e) $TsNHNH_2$, AcOH, HCl, DCM, 48 h, reflux, 74 %; (f) (i) Catecholborane, 0 °C; (ii) $NaOAc.XH_2O$, 16 h, reflux, 88 %; (g) p-TsOH, anhyd. DCM.



Scheme 3. Synthesis of *cis*-CBD isomers (A)[76] cis-(3S,4R)-CBD (4) and (B)[76] & (C)[77] cis-(3R,4S)-CBD (3). The synthesis of the *trans*-isomers are also shown in (A)[76] & (D)[77] (−)-CBD (1) and (B)[76] (−)-CBD (2). Reagents: (A) & (B) (a) $BF_3.OEt_2$, $MgSO_4$, EtOH, DCM, 4.5 h, rt, 55 % (36) and 1.5 % (39); (b) $PhNTf_2$, Et_3N, DCM, 16 h, rt, 86 % (37); (c) TMSCl, Et_3N, DCM, rt, 95 % (38); (d) (i) $C_5H_{11}MgBr$, $ZnBr_2$, LiBr, $PdCl_2(DPPF)$, THF, rt; (ii) H_2SO_4, H_2O, 1 h, rt, 90 % (1) and 94 % (4). (C) & D (a) Ethyl vinyl ether, PPTS, anhyd DCM, 5 h, 0 °C; (b) BuLi, TMEDA, anhyd DMF, THF/hexanes, 1 h, 0 °C to rt; (c) (i) NaOH, acetone, H_2O, 2.5 h, 50 °C; (ii) $MePPh_3Br$, BuLi, anhyd THF, 3 h, 0 °C to rt, 67 % (over four steps); (d) (R)-Cat_8, acrolein, benzylic acid, anhyd DCM, 16 h, −40 °C; (e) $NaClO_2$, KH_2PO_4, 2-methylbut-2-ene, ^{t}BuOH, H_2O, 0.5 h, rt; (f) MeI, K_2CO_3, DMSO, 2 h, rt, 59 % (47a, over three steps; 99.5:0.5 er); (g) MeLi, anhyd THF/Et_2O, 45 min, 0 °C, 58 % (48b, over 2 steps); (h) $SOCl_2$, Et_3N, THF, 20 min; (i) PPTS, MeOH, 0.5 h, rt, 58 % (3, over three steps) and 82 % (1, over two steps; 96:4 er); (j) MeONa, MeOH, 2 h, rt, (45c; 67 % over two steps; 96:4 er); (k) (+)C | | C (−), KI, anhyd. MeOH, 60 mA, 6F·mol^{-1}, 7 h, rt.

example, Jin et al. reported the synthesis of CIA001 (**62**), a CBD derivative with a triazole ring instead of *n*-pentyl group (Scheme 5A).[77] Its synthesis began with **56,** which was benzylated, reduced, and brominated to react with 1,2,3-triazole to yield **61**. Subsequent Friedel–Crafts reaction with the *trans*-isomer **5b** gave compound **62**. Additionally, the synthesis of KLS13019 (**70**), an acyl azetidine analog of CBD, was reported by Kinney et al. (Scheme 5B).[78] The azetidine intermediate **65** was formed via a Wittig reaction, acylated and subjected to a Friedel–-Crafts reaction with the *cis*-isomer **5a** to give the target compound **70**.

In 2021, Navarro et al. reported different (−)-*trans* derivatives of **1,**



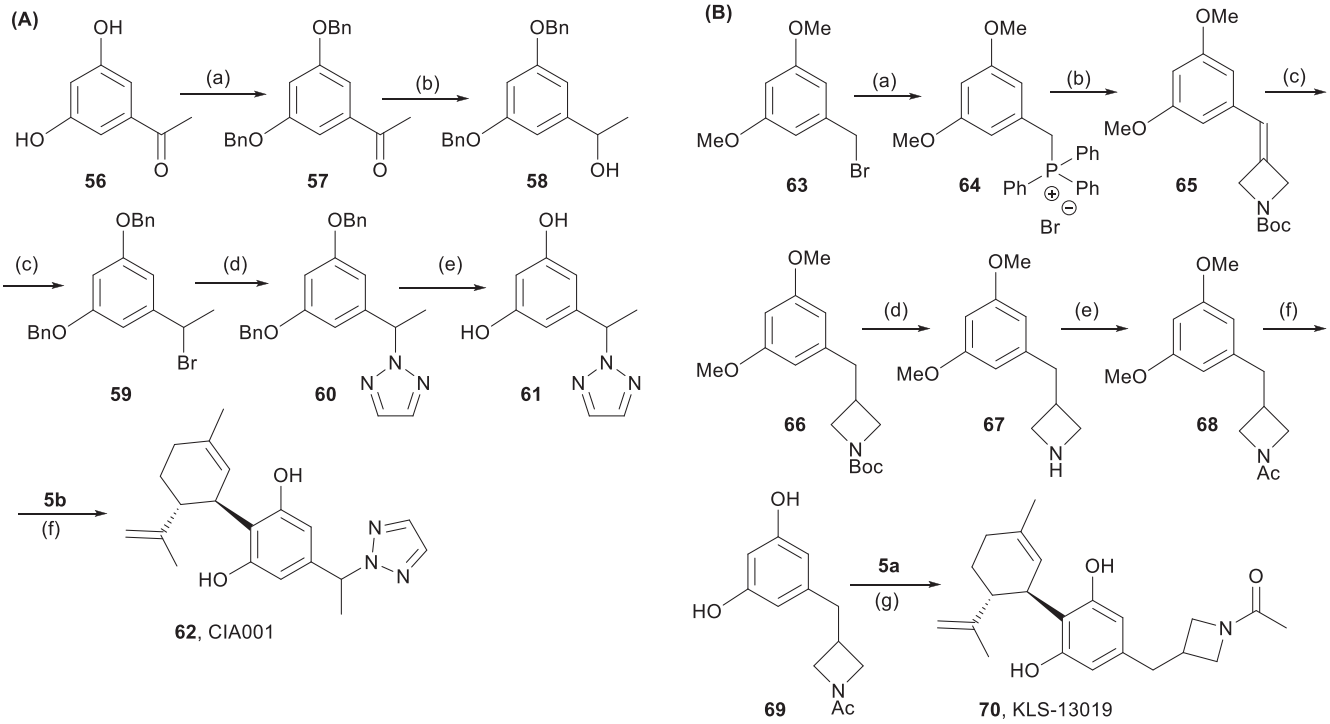
Scheme 4. Synthesis of compounds 54 (HU-446) and 55 and (HU-465).[78] Reagents: (a) PtO_2/H_2, EtOAc, 10 psi, rt, 98 %; (b) $BF_3{\cdot}OEt_2$, Al_2O_3, DCM, 60 %; (c) Ac_2O, pyridine, 16 h, rt, 100 %; (d) SeO_2, EtOH, 4 h, reflux, 54 %; (e) $NaBH_4$, EtOH, 1 h, reflux, 30 %.

varying the alkyl chain in region 3 (Scheme 6A).[79] These compounds were synthesized starting with the Wittig reaction of aldehyde **71**, followed by reduction and bromination to **74**. Friedel–Crafts reaction of **75** and de-bromination gave the compounds **77**–**80**. Region 2 and 3 modifications were conducted by Fiebich et al., who synthesized and evaluated the biological activities of (+)-*trans* derivatives of **2** (Scheme 6B), starting with *cis*- or *trans*-*p*-mentha-2,8-dien-1-ol (**81a** or **81b**).[80] This synthetic route involved a Friedel–Crafts reaction, a transesterification to give **84** followed by decarboxylation to give **2** and **85**. Furthermore, González-Mariscal et al. synthesized **1**, **2**, and the (+)-*trans*-(3*S*,4*S*) derivatives **83b** and **86** starting with *cis*-**81a** via a Friedel–Crafts reaction and transesterification (Scheme 6B).[81] Under similar conditions, the corresponding (−)-*trans* compounds **87**–**89** were obtained from **5a** or **5b**.[82]

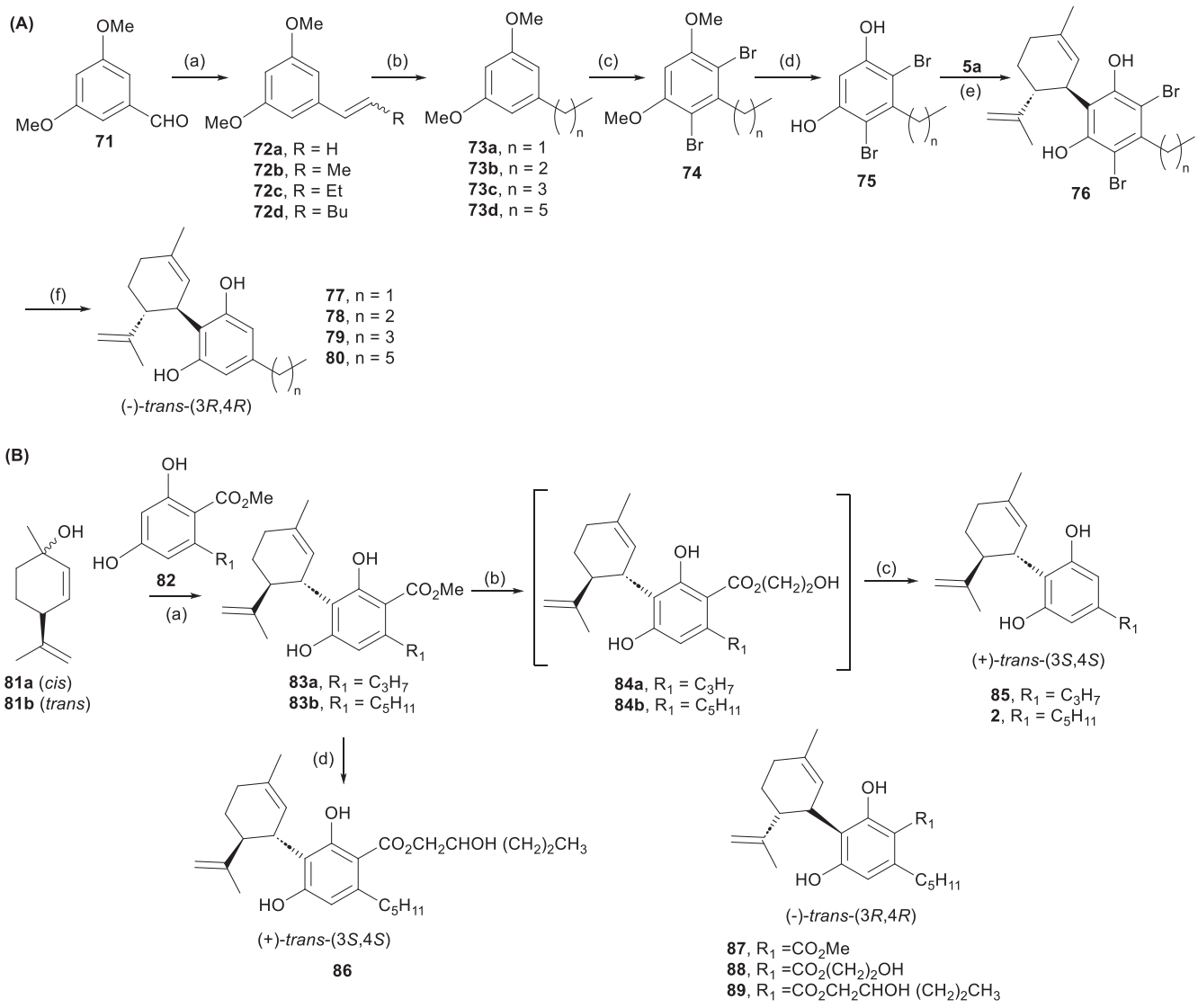
Enantiomerically pure compounds **1**, **2**, and several other (−)- and (+)-*trans* derivatives with modifications on region 3 as well as the cyclohexene ring were synthesized by Hanuš et al. (Scheme 7A).[55] By employing the representative Friedel–Crafts reaction of starting materials **90** and **91**, compound **92** was obtained and subsequently converted to the epoxide intermediate **94**. The bromo derivative **97** was obtained after three steps from **94** and acylation and deprotection steps gave the 7-hydroxy metabolites **100**–**103**. The corresponding 7-carboxy metabolites were obtained via the intermediate **95**, which was converted to the aldehyde **107** in four steps, oxidized to the carboxy and deprotected to give **109**–**112** (Scheme 7B).

Hanuš et al. and Smoum et al. in separate studies reported the synthesis of a novel CBD derivative **120** and its enantiomer **121**, respectively (Scheme 8A).[83,84] Compound **120** was synthesized starting from (+)-α-pinene (**113**), which was converted to (1*S*)-(+)-myrtenol **114**, while **121** was obtained from the counterpart of **114**, (1*R*)-(−)-myrtenol. Protection of hydroxyl group in **114**, followed by oxidation and reduction, gave the intermediate **117**. Friedel–Crafts alkylation of **117** with **91**, methylation, and deprotection gave the desired compounds **120** and **121** (Scheme 8A). Covalent analogs of **120** and **121**, that is, **130** (HU-308-NCS) and **131** (HU-433-NCS), were synthesized by Westphal et al. (Scheme 8B).[85] This involved a cross-coupling reaction of **122**, followed by the formation of dimethyl intermediate **124** and deprotection to give the halo-intermediate **125.** Friedel–Crafts reaction of intermediates **117** and **125a** or **125b**, subsequently led to **130** and **131**, respectively.

Kearney et al. demonstrated the synthesis of axially chiral cannabidiols (axCBDs) (Scheme 9).[86] The propargyl compound **133** was



Scheme 5. (A) Synthesis of compound 62 (CIA001), a triazole derivative of 1,[77] and (B) Synthesis of compound 70 (KLS-13019).[78] Reagents: (A) (a) BnBr, K_2CO_3, acetone, 24 h, reflux, 98 %; (b) $NaBH_4$, DCM/MeOH (20:1), 1.5 h, rt, 99 %; (c) PBr_3, anhyd Et_2O, 5 h, reflux, 98 %; (d) 1, 2, 3-Triazole, NaH, DMF, 24 h, 110 °C, 26 %; (e) Pd/C, H_2, MeOH, rt, 82 %; (f) p-TsOH, DCE, 2 h, rt, 21 %. (B) (a) PPh_3, toluene, 4 h, reflux, 97 %; (b) Azetidine carbonyl, *n*-BuLi, THF, 1 h, 0 °C to rt, 63 %; (c) Pd/C, H_2, EtOAc, 4 h, rt, 97 %; (d) TFA, DCM, 40 mins, 0 °C, 99 %; (e) CH_3COCl, Et_3N, DCM, 1 h, rt; 80 % (f) BBr_3, DCE, 3 h, rt, 51 %; (g) $BF_3{\cdot}Et_2O$, DCM/THF (4:1), 1 h, rt, 13 %.



Scheme 6. Synthesis of (A)[81] alkyl derivatives of (−)-CBD (1) and (B)[82,83] alkyl and ester derivatives of (+)-CBD (2). Reagents: (A) (a) RCH_2PPh_3Br, *n*-BuLi, anhyd THF, 0 °C to rt; 88 %, quantitative yield; (b) Pd/C, H_2, AcOH, MeOH, 24 h, up to 98 %; (c) NBS, DCM, 16 h, rt, quantitative yield; (d) BBr_3, DCM, 16 h, −10 °C to rt, up to 91 %; (e) p-TsOH, $MgSO_4$, anhyd DCM, 16 h, −35 °C to rt, up to 71 %, (f) Na_2SO_3, Et_3N, L-ascorbic acid, MeOH/H_2O, 24 h, 75 °C, 63 %. (B) (a) $BF_3{\cdot}OEt_2$, toluene, 30 °C, 70 %, (b) Ethylene glycol, KOH, 500 mbar, 5 h, 120 to 150 °C; (c) H_2SO_4, 40 °C; 34 % (99 % ee); (d) 1,2-Pentanediol, KOH, 500 mbar, 5 h, 120 to 150 °C, 99 % ee.

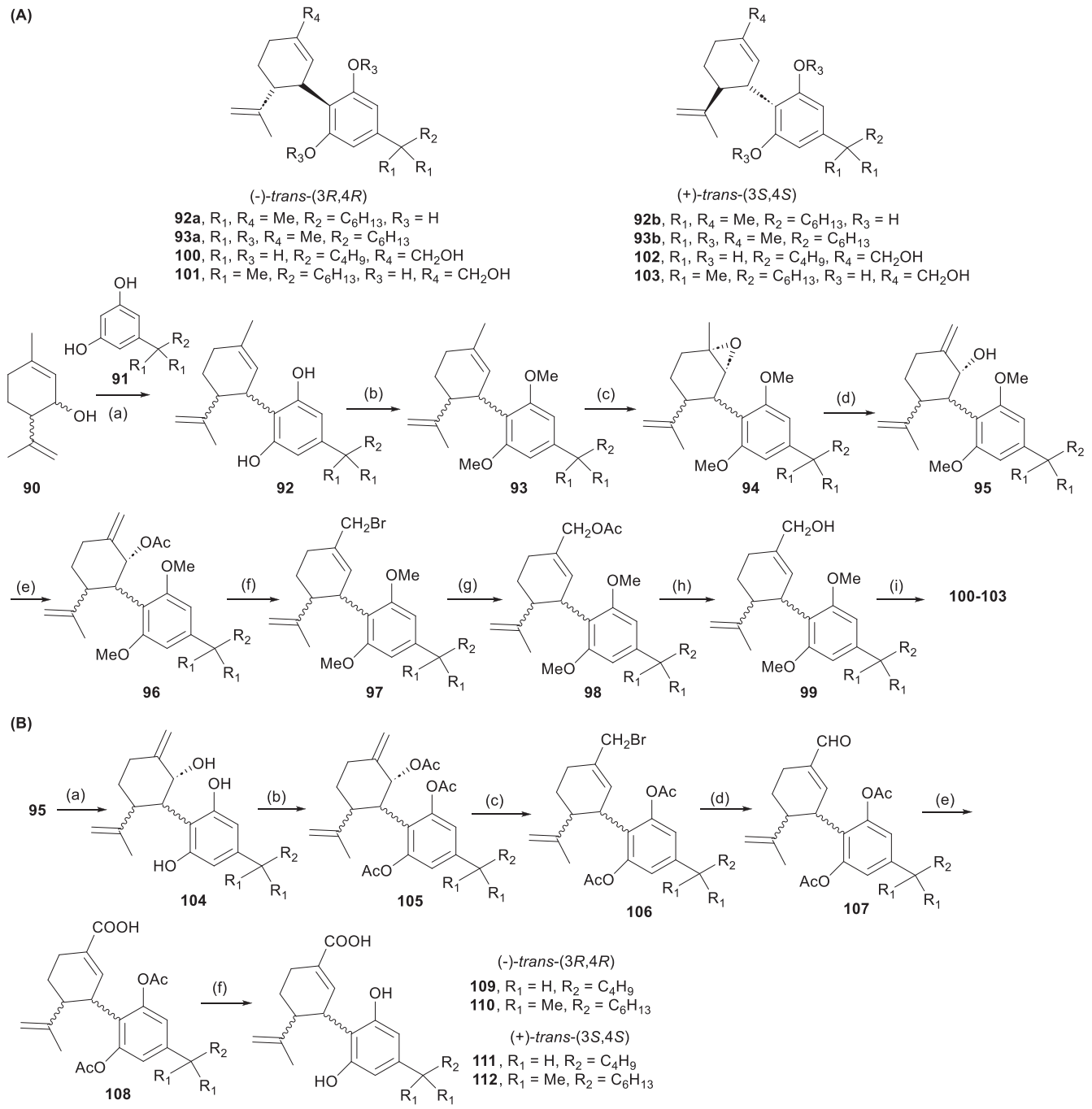
obtained via copper-catalyzed coupling, followed by a condensation to **134**, that was obtained as a mixture of *E* and *Z* isomers and carried forward to the next step without separation. Cyclization of **134** gave the tricyclic intermediate **135**, and mono-demethylation and reduction gave the axCBDs **137a** and **137b** as a mixture. It should be noted that the mixture was separated by supercritical fluid chromatography, but the absolute stereochemistry of the compounds was not determined.

5. Structure-activity relationships of CBD stereoisomers and their analogs

Biological activities of CBD derivatives are diverse and deserves to be closely examined. Table 1 summarizes these myriads of biological activities for ease of tracking. The development of stereoselective methods for the synthesis of CBD isomers, such as *trans*-CBD isomers **1** and **2**, has facilitated their pharmacological evaluation.[81] Among the four stereoisomers, the naturally abundant enantiomer (−)-CBD (**1**) has been extensively studied for its pharmacological properties and clinical use.[53,87,88] The unnatural enantiomer (+)-CBD (**2**) has demonstrated anticonvulsant activity in animal models, similar to the natural analog **1**.[89,90] Interestingly, **2** exhibited higher affinities for cannabinoid receptors *in vitro* than **1**.[55,56,89]

Recently, *in vitro* biological activities of **1** and **2** in autaptic hippocampal neurons and in CHO-K1 cells were reported.[72] The K_i of **2** for displacing CP-55,940 at CB_1R was five-fold lower than that for **1** and is about 10 times more potent in inhibiting depolarization-induced suppression of neuroexcitation. Interestingly, **2** also inhibited CB_1R suppression of cyclic adenosine monophosphate (cAMP) accumulation and activated the sphingosine-1 phosphate (S1P) receptors, S1P1 and S1P3. These data suggested that the signaling profiles of the CBD enantiomers could differ in their activities in a pathway-specific manner.[72]

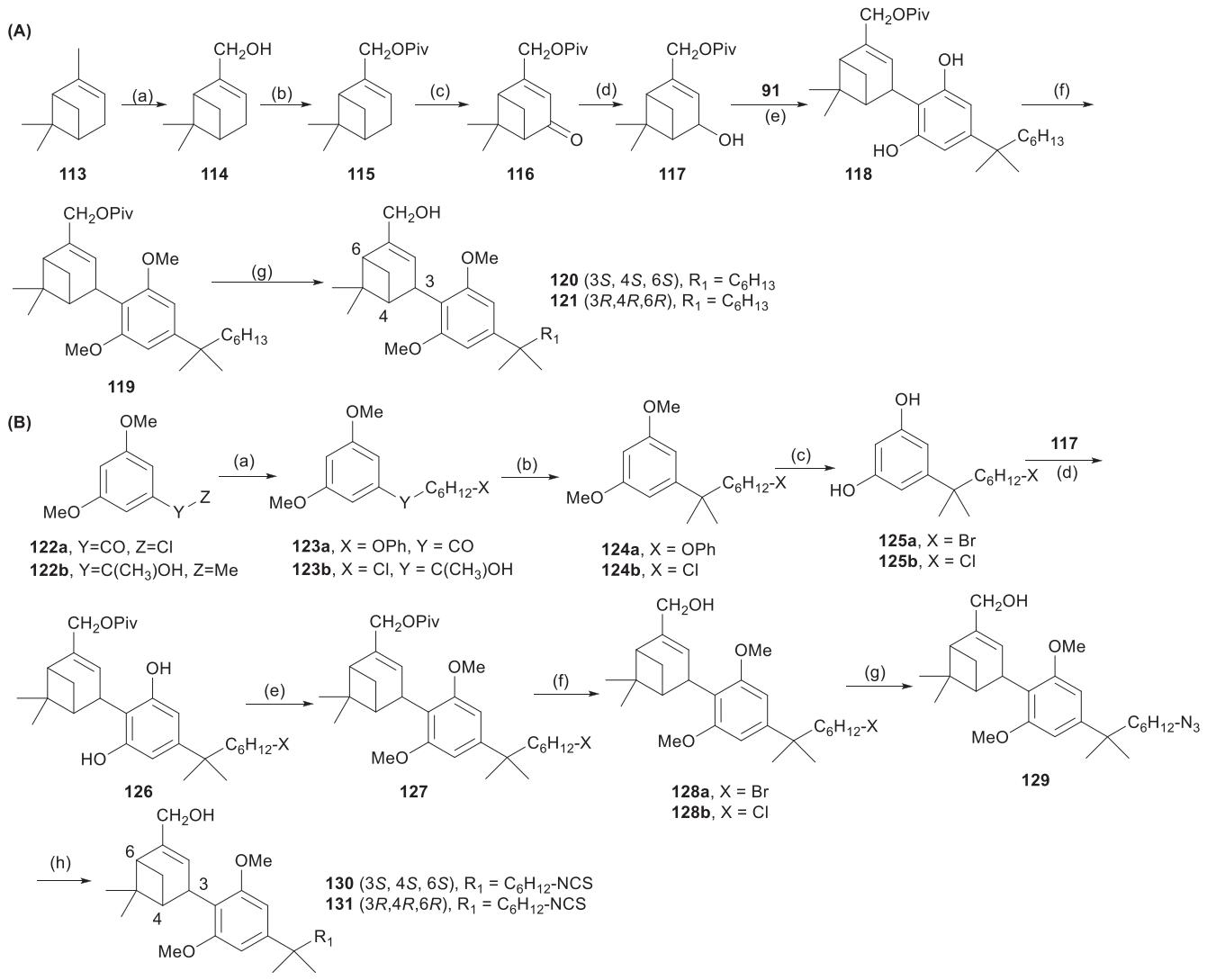
Biological evaluations of 8,9-dihydro-7-hydroxy-CBD derivatives **54** (HU-446) and **55** (HU-465), possessing (−) and (+) stereochemistry, respectively, demonstrated that **54** has very low affinity toward CB_1R and CB_2R, while **55** binds to both CB_1R and CB_2R with high addinity at nanomolar concentrations (K_i = 76.7 ± 5.8 nM and 12.1 ± 2.3 nM, respectively).[76] The anti-inflammatory effects of these newly synthesized derivatives on activated MOG_{35-55}-specific mouse



Scheme 7. Synthesis of 7-hydroxy metabolites derivatives (A) and 7-carboxy metabolites (B) of (−) and (+)-CBD.[57] Reagents: (A) (a) $BF_3{\cdot}OEt_2$, basic Al_2O_3, anhyd DCM, rt to 40 °C, up to 55 %; (b) MeI, K_2CO_3, DMF, 4 h, rt, 96 %; (c) 3-Chloroperbenzoic acid, DCM, 0 °C, 30 min, 70 %; (d) *N*-Cyclohexylisopropylamine, *n*-BuLi, MeMgBr, anhyd toluene, 3 h, 0 to 40 °C, 97 %; (e) Ac_2O, pyridine, 18 h, rt, quant yield; (f) TMSBr, anhyd DCM, 4 h, rt, 90 %; (g) $(n\text{-}Bu)_4NH_4OAc$, acetone, 2 h, reflux, 92 %; (h) aq NaOH, EtOH, 1 h, reflux, 94 %; (i) MeMgI, anhyd Et_2O, 45 min, 42 %. (B) (a) MeMgI, anhyd Et_2O, 45 min, 210 °C, 58 %; (b) Ac_2O, pyridine, 18 h, rt, quantitative; (c) TMSBr, ZnI_2, anhyd DCM, 4 h, rt, 90 %; (d) K_2CrO_4, anhyd HMPA, 2 h, 110 °C; 32 %; (e) $NaClO_2$, KH_2PO_4, *t*-BuOH, 5 h, rt, 85 %; (f) $NaBH_4$, EtOH, 1 h, reflux, 92 %.

encephalitogenic T cells (TMOG) driving EAE/MS-like pathologies were also investigated. Both **54** and **55**, at 5 and 10 μM, respectively, significantly decreased the proliferation of encephalitogenic TMOG cells and prevented them from releasing neurotoxic IL-17 in the presence of $MOG_{35\text{-}55}$ antigen. Furthermore, **54** and **55** decreased TMOG proliferation via a CB_1R/CB_2R independent mechanism and ameliorated inflammation induced by TMOG.[76]

Heterocycles, particularly those that contain nitrogen are ubiquitous in many pharmaceutical drugs due to their ability to modify hydrophilicity, hydrogen bonding and solubility. Compounds with heterocyclic modifications in region 3 of **1**, were evaluated for their anti-neuroinflammatory *in vitro* activities in a lipopolysaccharide (LPS)-induced proinflammatory model using immunocompetent BV2 cells.[77] The triazole-containing compound **62** stabilized the tetramer formation of pyruvate kinase M2 (PKM2) dimer, and potently inhibited its nuclear translocation with an $IC_{50} = 2.5 \pm 0.7$ μM, a potentially novel activity for a CBD analog.[77] In essence, as a result of this structural modification, **62** displayed 4.9-fold increase in anti-neuroinflammatory activity and 6.8-fold lower toxicity in comparison to **1**.[77] The acyl azetidine derivative KLS-13019 (**70**) was also evaluated in various assays targeting



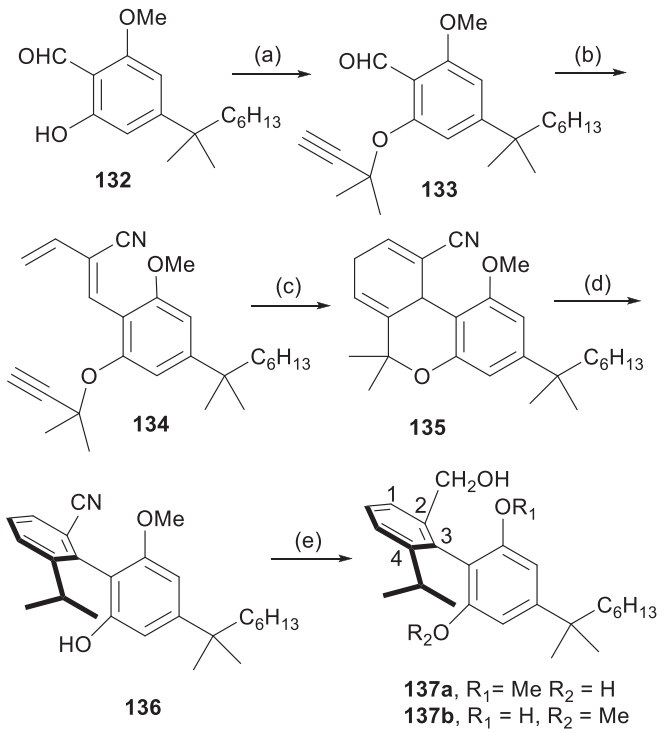
Scheme 8. Synthesis of compounds 120 (HU-308) and 121 (HU-433) (A)[86,87] and their NCS derivatives 130 and 131 (B)[88]. Reagents: (A) (a) Oxidation (b) Pivaloyl chloride, pyridine, overnight, 0 °C to rt, 91 %; (c) Na_2CrO_4, Ac_2O, 72 h, 35 °C (or) CrO_3, acetonitrile, 0 °C then *t*-BuOOH, 1 h, rt, 30 %; (d) $LiAlH[OC(CH_3)_3]_3$, anhyd THF or $NaBH_4$, EtOH, 4 h, 91 %; (e) p-TsOH, anhyd DCM, 1.5 h, rt, 43 %; (f) K_2CO_3, MeOH or MeI, K_2CO_3, DMF, 16 h, rt, 67 %; (g) LiAlH, Et_2O, reflux, 80 %. (B) (a) $LiCl{\cdot}BrMgC_6H_{12}$-X (X = OPh or Cl), $Fe(acac)_3$, anhyd THF, 45 mins, −78 °C to rt (or) anhyd THF, −78 °C, 90 %; (b) $TiCl_4$, $ZnMe_2$, DCM, 16 h, rt (or) (i) HCl, 16 h, rt; (ii) $AlMe_3$, DCM, 6 h, rt, 67 %; (c) BBr_3, DCM, 0 °C, 95 %; (d) p-TsOH·H_2O, CH_2Cl_2, rt, 86 %; (e) Me_2SO_4, K_2CO_3, acetone, 16 h, rt, 73 %; (f) DIBAL-H, CH_2Cl_2, 15 min, 0 °C, 94 %; (g) NaN_3, DMF, rt (or) NaN_3, DMSO, 16 h, 50 °C; (h) PPh_3, CS_2, THF, 16 h, 40 °C, 97 %.

neurotoxicity. In these assays, **70** showed potent activity in preventing neuronal damage with EC_{50}s in the range of 50 ± 10 to 80 ± 30 nM and was 50-fold more potent and > 400-fold less toxic than **1**.[78]

The (−)-*trans* CBD derivatives **77**–**80**, with varying alkyl chains in region 3, exhibited negative and positive allosteric modulatory (NAM and PAM, respectively) activities on CB_2R. Compounds **77** and **78** behaved as PAMs, and compounds **79** and **80** behaved as NAMs.[79] (+)-*Trans* CBD compounds **2** and **85**, also possessing alkyl chains of different lengths, were likewise evaluated *in vitro*. Of these derivatives, compound **85** was one of the most active molecules, acting as an antagonist at CB_1R. Compound **85** was also shown to be more efficient and selective than **2** and **78**, with binding affinities at CB_1R and CB_2R of 294 nM and 33.1 nM, respectively.[80]

Other (+)-*trans* CBD derivatives with two modifications on the resorcinol ring, namely alkyl chain length and ester, showed better binding and functional activities compared to their corresponding (−)-*trans* enantiomers. Compounds **83b, 84b** and **86** displayed higher CB_1R and CB_2R binding and functional activities compared to complementary enantiomers **87**–**89**.[80–82] Compound **86** with a 2-hydroxy pentyl ester displayed strong CB_1R and CB_2R binding affinities with K_i values of 3.1 ± 1.1 nM and 0.8 ± 0.1 nM, respectively.[81] Compound **86** was among the most active compounds, acting as an antagonist at CB_1R (IC_{50} = 0.21 ± 0.07 μM), and as an agonist at CB_2R (EC_{50} = 0.09 ± 0.78 μM).[81] *In vivo* experiments involving compound **86** demonstrated a prevention of the development of neuropathy in diabetic mice. In a mouse model of glucose intolerance and hyperglycemia caused by streptozotocin (STZ), **86** lowered these effects by decreasing NF-κB activation.[81] Compound **86** also prevented STZ-induced apoptosis in mouse islets, reducing STZ-induced kidney lesions as well as renal fibrosis and $CD3^+$ T cell infiltration.[81] Furthermore, **2**, **78,** and **84b** were found to be potent anti-inflammatory agents, while (+)-CBD **2** and **86** were found to exhibit immunomodulatory activities.[80,91]

CBD derivatives with modifications in both region 3 of the resorcinol ring as well as the cyclohexene substituent have also been pre-clinically investigated. CBD metabolites and dimethylheptyl intermediates were evaluated for their activities at the cannabinoid receptors. Data indicated that the (−)-*trans* derivatives with (3*R*,4*R*) stereochemistry (compounds **92a, 93a**, **100**, **101**, **109**, and **110**) bound CB_1R and CB_2R



Scheme 9. Synthesis of axially-chiral cannabidiols, 137a and 137a.[89] Reagents: (a) 3-Chloro-3-methylbut-1-yne, Cu catalyst; (b) But-3-ene-nitrile, $TiCl_4$, Et_3N (c) LiHMDS, DMSO, 1 h, rt; (d) NaSEt, DMF, 120 °C; 44 %; (e) DIBAL-H, $NaBH_4$, 28 % (racemate).

with poor affinity, whereas the (+)-*trans*-(3*S*,4*S*) derivatives (compounds **92b, 93b**, **102**, **103**, **111**, and **112**) showed potent binding to CB_1R but weaker binding to CB_2R. For example, compound **92a** was bound to CB_1R and CB_2R with K_is of >10 μM and 1.8 μM, respectively, while its enantiomer **92b** was bound with K_is of 17.4 ± 1.8 nM and 211 ± 23 nM to CB_1R and CB_2R, respectively.[55,92] In the 7-hydroxy series, **103** binds with K_is of 2.5 ± 0.03 nM and 44.0 ± 3.12 nM to CB_1R and CB_2R, respectively, while the corresponding values for its enantiomer **101** are significantly higher, 4,400 nM and 671 nM, respectively.[55,92]Although all (+)-*trans* analogs bound to CB_1R and CB_2R and exhibited arrested defecation in mice, only **103** showed centrally-mediated activity.[92] The effects of **92b** and **103** were partially antagonized by the CB_1R antagonist SR141716, but not by the CB_2R antagonist SR144528, and had no effect on CB_1R (−/−) mice.[92] Compound **102b** also inhibited the peripheral pain response and arachidonic acid-induced inflammation of the ears.[55,92]

While compounds **1** and **2** stimulated the TRPV1 receptor with EC_{50} of 3.5 ± 0.3 μM and 3.2 ± 0.4 μM, respectively, the CBD metabolites and dimethylheptyl analogs did not.[56] However, the (+)-CBD dimethylheptyl compounds **92b** and **103**, along with **1** and **2**, increased the levels of endogenous anandamide (AEA, arachidonoylethanolamide) by inhibiting of [^{14}C]-AEA by rat basophilic leukaemia (RBL ± 2H3) cells with IC_{50} values of 10.0 ± 1.2 μM, 7.0 ± 1.2 μM, 22.0 ± 1.7 μM, and 17 ± 1.6 μM, respectively.[56] Those results imply that the dimethylheptyl group plays an important role in receptors and cell responses.

The novel bridged CBD derivative **120** (HU-308) with a (3*S*,4*S*,6*S*) configuration demonstrated high selectivity as an agonist for CB_2R, with EC_{50} of 5.57 nM.[83] Additionally, **120** inhibited the release of nitric oxide (NO) and pro-inflammatory cytokines, thus reducing the inflammatory response.[93] Compound **120** was shown to reduce striatal neuroinflammation and development of levodopa-induced dyskinesia (LID) in Parkinson's disease, as well as other neuroinflammatory conditions.[93] In mice suffering from collagen-induced arthritis (CIA), administration of **120** resulted in reduced synovial inflammation and production of anti-type II collagen antibodies. Administration of 120 also inhibited the production of pro-inflammatory cytokine interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) by peritoneal macrophages.[94] Compound **120** reduced oxidative stress, inflammatory responses and apoptosis by activating CB_2R, particularly in a mouse model of liver ischemia/reperfusion (I/R) injury, when administered prophylactically and immediately after the onset of ischemia.[95].

Moreover, **120** demonstrated anti-inflammatory, bone-protecting, and homeostatic effects on oral tissues in LPS-induced periodontitis.[96] In adolescent mice, **120** was associated with an increase in head twitch response (HTR), suggesting a potential role in motor tics in children.[97] Sex differences were observed, particularly in the prevalence of TS in males.[84] Compound **120** attenuated nausea and vomiting in animal models without causing psychoactive side effects[98] and promoted osteoblast proliferation due to its activity as a CB_2R agonist.[99] Activation of CB_2R by **120** in reactive microglia in the spinal cord of transgenic mouse models of Amyotrophic Lateral Sclerosis (ALS) preserved motor neurons and may potentially assist in slowing disease progression.[100]

On the other hand, compound **121** (HU-433), — the enantiomer of **120** — has a (3*R*,4*R*,6*R*) configuration and showed lower CB_2R binding affinity compared to that of **120**, however, it significantly increases bone anabolism and anti-inflammatory activity.[84] The difference in affinities of **120** and **121** may be due to their orientations of the bridging group in the binding pockets of the receptor.

To explore high-affinity fluorescence probes for CB_2R, the NCS derivatives **130** (HU-308-NCS) and **131** (HU-433-NCS) of compounds **120** and **121**, respectively, were evaluated *in vitro*. It was envisioned that the presence of the NCS group in **130** and **131** would promote irreversible binding to CB_2R by forming a covalent bond with the conserved residue Cys6.47, a favourable feature for such probes; however, this was not observed.[85]

Axially chiral cannabidiols are so-called based on the relocation of the C1 methyl group to the C2 position. This change results in rotational and angular restrictions about the biaryl-link, thereby forming three-dimensional structures (Scheme 9).[86,101] Single bond rotational restrictions lead to atropisomerism, and activity and affinity at receptors may be enhanced because of this structural change.[86] In functional activity assays involving [^{35}S]GTPγS (native G protein activation) and TRUPATH (Gαi1β3γ9 protein activation), Kearney et al. demonstrated that the racemic axial compound **137** showed hCB_2R agonism, with 7.4 fold potency (over hCB_1R) to stimulate [^{35}S]-GTPγS binding, while (−)-CBD **1** had no efficacy for hCB_1R or hCB_2R in either assay.[86] Furthermore, it was shown that once axial enantiomers **137a** and **137b** (absolute stereochemistry undetermined) were separated, there was no obvious difference in affinity at hCB_1R affinity. However, at hCB_2R, **137b** displayed 17-fold selectivity over hCB_1R and demonstrated 2.3-fold better affinity (278 nM) than that for **137a** (642 nM).[86]

6. Conclusions

Natural CBD, its stereoisomers, and its derivatives offer a significant structural diversity centered around two chiral centers and a number of positions for derivatization offering significant chemical diversity. Broadly, *cis* and *trans* isomers are defined, and *trans* isomers have been relatively easier to access synthetically. While the molecular and pharmacological properties of *cis*-CBD isomers are currently unknown, there are very encouraging data on *trans*-isomers. When compared to the natural (−)-*trans*-CBD isomer, its enantiomeric derivatives such as (+)-CBD (**2**) have been found to have higher potency at cannabinoid receptors. Derivatives with ester substitutions on the resorcinol ring of (+)-CBD also showed high selectivity toward both CB_1R and CB_2R. Replacement of the resorcinol *n*-pentyl chain of (+)-CBD with dimethylheptyl, as well as hydroxy and carboxy substitutions at C7 position of the terpene ring of CBD led to derivatives that were also selective for CB_1R. Furthermore, (+)-CBD derivatives with a cyclized C6-C8 terpene moiety, showed high selectivity for CB_2R. Although (−)-CBD and

Table 1
Receptor activities of CBD stereoisomers and their analogs.

Compound	Stereochemistry (Compound #)	K_i (nM)		CB_1R/CB_2R Selectivity	Other Targets and Activity (μM)	References
		CB_1R	CB_2R			
CBD	(−)-*trans*-(3*R*,4*R*) (**1**)	>1000	>1000	–	$NaV_{1.7}$: Inhibition; 1.82 ± 0.10[b] GPR55: Antagonist; 0.445 ± 0.67[b] *ENT*-1: Inhibition; 0.250[c] 5-HT_{1A}: Agonist; 16[a] A_{1A}: Potential agonist; CBD-antiarrhythmic effect is blocked by the adenosine A1 receptor antagonist DPCPX A_{2A}: Potential agonist; CBD-immunosuppression is blocked by a A_{2A} adenosine receptor antagonist ZM 241385 D2: Partial agonist; D2 High 0.066[c]; D2 Low 2.8[c] PPARγ: Potential agonist; CBD-reactive gliosis is blocked by a selective antagonist of PPARγ receptors, GW9662 FAAH: Inhibition; 27.5 ± 1.7[b] VR1: Agonist; 3.2 ± 0.4[a] AMT: 22 ± 1.7[b] TRPV2: Agonist; 1.25 ± 0.23[a] TRPA1: Agonist; 0.11 ± 0.05[a] TRPM8: Antagonist; 0.06 ± 0.01[b] TRPV1: Agonist; 1.0 ± 0.1[a]	4–7,56,72
	(+)-*trans*-(3S,4S) (**2**)	842 ± 36	203 ± 16	4.1	FAAH: Inhibition; 63.5 ± 4.2[b] VR1: 3.5 ± 0.3 (EC_{50}(μM)) AMT: 17.0 ± 1.6[b]	56,72
HU-446	(−)-*trans*-(3*R*,4*R*) (**54**)	>1000	>1000	–	–	76
HU-465	(+)-*trans*-(3S,4*S*) (**55**)	76.7 ± 5.8	12.1 ± 2.3	6.3	–	
CIA001	(−)-*trans*-(3*R*,4*R*) (**62**)	–	–	–	BV2: 2.5 ± 0.7[b]	77
KLS-13019	(−)-*trans*-(3*R*,4*R*) (**70**)	–	–	–	Neuroprotective: 50 ± 10 to 80 ± 30 nM[a]	78
CBDV	(−)-*trans*-(3*R*,4*R*) (**78**)	>1000	574.2 ± 146	–	–	79–81
	(+)-*trans*-(3S,4*S*) (**85**)	294	33.1	8.9		
CBD-ME	(−)-*trans*-(3*R*,4*R*) (**88**)	–	–	–	–	80
	(+)-*trans*-(3S,4*S*) (**83b**)	345	28	12.3		
CBD-GE	(−)-*trans*-(3*R*,4*R*) (**90**)	>1000	374.5 ± 47.7	–	–	91
	(+)-*trans*-(3S,4*S*) (**84b**)	359	12.9	27.8		80
CBD-HPE	(−)-*trans*-(3*R*,4*R*) (**89**)	538 ± 54	66.7 ± 13.1	8.1	–	80,81,91
	(+)-*trans*-(3S,4*S*) (**87**)	3.1 ± 1.1	0.8 ± 0.1	3.9		
DMH-CBD	(−)-*trans*-(3*R*,4*R*) (**92a**)	>1000	>1000	–	AMT:14.0 ± 1.3[b]	55,56,92
	(+)-*trans*-(3S,4*S*) (**92b**)	17.4 ± 1.8	211 ± 23	0.08	AMT:10.0 ± 1.2[b]	
7-OH-DMH-CBD	(−)-*trans*-(3*R*,4*R*) (**101**)	>4000	671 ± 12	–	AMT12.5 ± 2.0[b]	
	(+)-*trans*-(3S,4*S*) (**103**)	2.5 ± 0.03	44.0 ± 3.1	0.05	AMT;7.0 ± 1.2[b]	
DMH-CBDD	(−)-*trans*-(3*R*,4*R*) (**93a**)	>1000	>1000	–	–	
	(+)-*trans*-(3S,4*S*) (**93b**)	>1000	>1000			
7-OH-CBD	(−)-*trans*-(3*R*,4*R*) (**100**)	>1000	>1000	–	–	
	(+)-*trans*-(3S,4*S*) (**102**)	5.3 ± 0.5	101.0 ± 5.1	0.05		
7-COOH-CBD	(−)-*trans*-(3*R*,4*R*) (**109**)	>1000	>1000	–	–	

(*continued on next page*)

Table 1 (*continued*)

Compound	Stereochemistry (Compound #)	K_i (nM)		CB_1R/CB_2R Selectivity	Other Targets and Activity (μM)	References
		CB_1R	CB_2R			
	(+)-*trans*-(3S,4*S*) (**111**)	13.2 ± 0.4	312.8 ± 15	0.04		
7-COOH-DMH-CBD	(−)-*trans*-(3*R*,4*R*) (**110**)	>1000	>1000	–	–	
	(+)-*trans*-(3S,4*S*) (**112**)	5.8 ± 0.7	155.5 ± 5.3	0.03		
HU-308	3*S*,4*S*,6*S* (**120**)	>10000	22.7 ± 3.9	454	–	83–85,96
HU-433	3*R*,4*R*,6*R* (**121**)	>1000	>1000	–	–	
HU-308-NCS	3*S*,4*S*,6*S* (**130**)	2670	13.1	203	–	
HU-433-NCS	3*R*,4*R*,6*R* (**131**)	>1000	121	–	–	
axCBD	*ax*CBD-1 (**137a**)	>1000	0.64	–	–	86
	*ax*CBD-2 (**137b**)	>1000	0.28	17		

A1A, adenosine A1 receptor; A2A, adenosine A2 receptor; AMT, anandamide membrane transporter; BV2, microglial cell line; CB1, cannabinoid receptor type 1; CB2, cannabinoid receptor type 2; D2, Dopamine receptor D2; ENT1, equilibrative nucleoside transporter 1; FAAH, fatty acid amide hydrolase; GPR6, G-protein-coupled receptor 6; GPR55, G-protein-coupled receptor 55; 5-HT1A, serotonin receptor 1A; PPARγ, peroxisome proliferator-activated receptor gamma; TRPA1, transient receptor potential ankyrin 1; TRPM8, transient receptor potential cation channel subfamily M (melastatin) member 8; TRPV1, transient receptor potential vanilloid type 1; VR1, vanilloid receptor type 1.

[a] EC50.

[b] IC50.

[c] K_i.

(+)-CBD isomeric derivatives were more effective against a variety of disease models, (+)-CBD isomeric derivatives demonstrated good potential for the treatment of various neuroinflammatory disorders.

While advancements have been made in increasing the structural diversity of CBD, there is a significant opportunity for robust stereoselective and non-stereoselective synthetic methodologies to obtain enantiomers of CBD derivatives. Future research in CBD synthesis — especially of diverse enantiomeric analogs — needs to leverage what is already known to drive further exploration of structure–activity relationships and biological evaluations, thus paving the path for the development of novel CBD therapeutics.

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CRediT authorship contribution statement

Vajja Krishna Rao: Writing – review & editing, Writing – original draft. **Melissa M. Lewis-Bakker:** Writing – review & editing. **Ewa Wasilewski:** Writing – review & editing. **Hance A. Clarke:** Writing – review & editing, Funding acquisition. **Lakshmi P. Kotra:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Lakshmi P. Kotra reports financial support was provided by Canadian Institutes of Health Research. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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