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# Enantioselective Total Synthesis of (−)-$\Delta^8$-THC and (−)-$\Delta^9$-THC via Catalytic Asymmetric Hydrogenation and $S_NAr$ Cyclization

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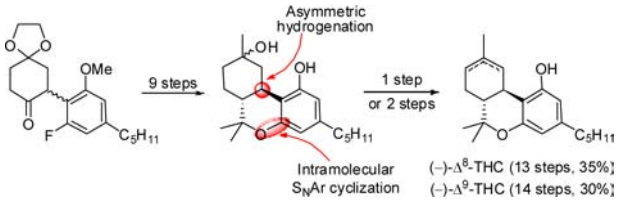
## ABSTRACT




**The highly efficient asymmetric total syntheses of (−)-$\Delta^8$-tetrahydrocannabinol ((−)-$\Delta^8$-THC) (13 steps, 35%) and (−)-$\Delta^9$-tetrahydrocannabinol ((−)-$\Delta^9$-THC) (14 steps, 30%) have been developed by using ruthenium-catalyzed asymmetric hydrogenation of racemic α-aryl cyclic ketones via dynamic kinetic resolution and intramolecular $S_NAr$ cyclization.**

Many biologically active natural products and pharmaceutical agents contain chiral hexahydro-6,6-dimethyl-6*H*-benzo[*c*]chromene motifs (Figure 1). (−)-$\Delta^9$-Tetrahydrocannabinol ((−)-$\Delta^9$-THC), isolated from *Cannabis sativa L.* in 1964,[1] is one of the most well-known examples of this class of tricyclic compounds and has been used as a medicine under the trademarks of Marinol and Sativex for the treatment of cancer, nausea, and vomiting during chemotherapy and spasticity in patients with multiple sclerosis.[2] (−)-$\Delta^8$-Tetrahydrocannabinol ((−)-$\Delta^8$-THC), also isolated from *Cannabis sativa L.*,[3] is a double bond isomer of (−)-$\Delta^9$-THC and functions similarly to (−)-$\Delta^9$-THC pharmacologically. (+)-Conicol[4] and its epimer (+)-epiconicol,[5] isolated from ascidians *Aplidium conicum* and *Synoicum castellatum*, are also tetrahydrocanabinol derivatives, and the latter exhibits mild cytotoxic activities against P388 (murine leukemia), A549 (human lung cacinoma), etc. Moreover, the natural bibenzyl tetrahydrocannabinol (−)-perrottetinene,[6] isolated from the liverwort plant *Radula marginata*, and synthetic pharmaceutical agents such as 1-deoxyl-$\Delta^8$-tetrahydrocannabinols JWH-051 and JWH-057[7] also contain a chiral hexahydro-6,6-dimethyl-6*H*-benzo[*c*]chromene structure. Thus, the enantioselective construction of the chiral hexahydro-6,6-dimethyl-6*H*-benzo[*c*]chromene motif constitutes a basic requisite for the stereoselective synthesis of tetrahydrocanabinol derivatives (and/or analogues).

Although considerable efforts have been devoted to the development of the methodology for the synthesis of chiral hexahydro-6,6-dimethyl-6*H*-benzo[*c*]chromenes, most of the methods reported in the literature produced these

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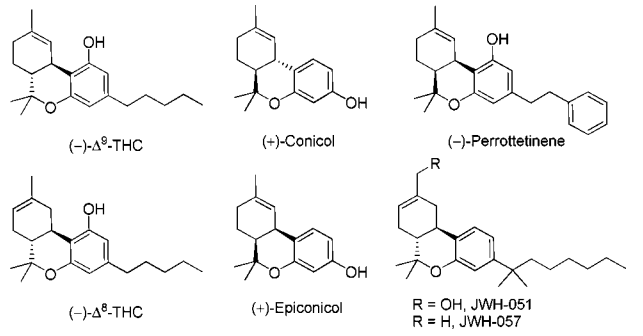
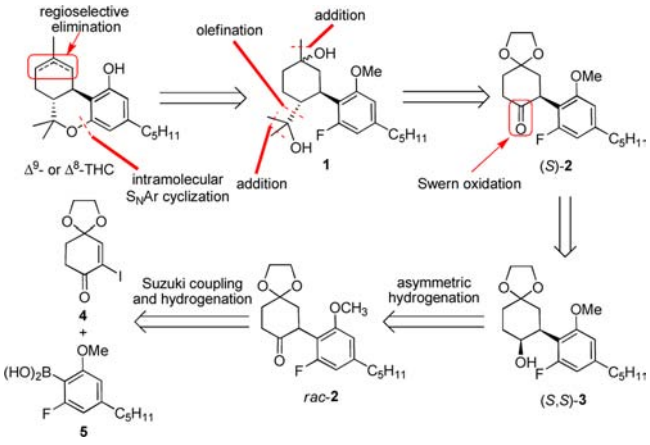



**Figure 1.** Natural products and pharmaceutical agents contained chiral hexahydro-6,6-dimethyl-6*H*-benzo[*c*]chromene motifs.

tricyclic compounds either in racemic form or from chiral building blocks.[8] Very few examples used asymmetric catalysis to construct the chiral hexahydro-6,6-dimethyl-6*H*-benzo[*c*]chromene structure. Evans et al.[9] reported an asymmetric synthesis of (+)-$\Delta^9$-THC via an enantioselective Diels–Alder reaction catalyzed by copper(II) complexes of chiral bis(oxazoline) ligands. Trost and Dogra[10] applied a molybdenum-catalyzed asymmetric allylic alkylation reaction in the synthesis of (−)-$\Delta^9$-THC. Recently, Hong et al.[11] reported a total synthesis of (+)-conicol by using an asymmetric organocatalytic cascade reaction.

The catalytic asymmetric hydrogenation is one of the most versatile and powerful tools for the preparation of optical compounds and has been successfully applied to the total synthesis of biologically active natural products and pharmaceutics.[12] Recently, we developed highly efficient ruthenium-catalyzed asymmetric hydrogenations of racemic α-substituted ketones and aldehydes via dynamic kinetic resolution (DKR)[13] for the preparation of chiral alcohols with one or two continuous stereocenters, which have been successfully applied to the enantioselective total synthesis of natural products such as (−)-galanthamine[14] and pharmaceutical agents such as (−)-CP-55940.[15] Herein, we reported a highly efficient asymmetric total synthesis of (−)-$\Delta^9$-THC and (−)-$\Delta^8$-THC by using catalytic asymmetric hydrogenation of ketones via DKR and intramolecular $S_NAr$ cyclization as key steps.

**Scheme 1.** Retrosynthetic Analysis of (−)-$\Delta^8$-THC and (−)-$\Delta^9$-THC




The retrosynthetic analysis suggested that the target molecules (−)-$\Delta^8$-THC and (−)-$\Delta^9$-THC could be synthesized from the precursor **1** using an intramolecular $S_NAr$ cyclization to construct the benzopyran ring and a regioselective elimination of $H_2O$ to form the double bond (Scheme 1). The diol **1** was expected to be obtained from optically active α-arylcycloketone (*S*)-**2** via several steps including olefination and the addition of a methyl metal reagent such as MeMgBr to the carbonyl groups of both the ketone and ester group. According to our previous procedure for the synthesis of potent cannabinoid receptor agonist (−)-CP-55940,[15] the chiral α-aryl-1,4-cyclohexanedione monoethylene acetal (*S*)-**2** could be easily obtained from the Suzuki cross-coupling of 2-iodo-1,4-cyclohexanedione monoethylene acetal (**4**) with fluorine-substituted phenylboronic acid **5** followed by a palladium-catalyzed hydrogenation, ruthenium-catalyzed asymmetric hydrogenation via DKR, and Swern oxidation.

Initially, we attempted to construct the benzopyran ring by using $ZnBr_2$-promoted intramolecular cyclization according to the literature method.[16] As a model reaction, the asymmetric hydrogenation of racemic 2-(2,6-dimethoxyphenyl)cyclohexanone catalyzed by $RuCl_2$((*S*)-SDP)((*R*,*R*)-DPEN) (($S_a$,*R*,*R*)-**6**)[17] was carried out. This hydrogenation reaction was found to be very difficult and impractical presumably due to the steric hindrance caused by two *ortho*-methoxy groups in the substrate.[18] In contrast, the α-arylcyclohexanones with one *ortho*-methoxy group were hydrogenated smoothly with the same catalyst to produce

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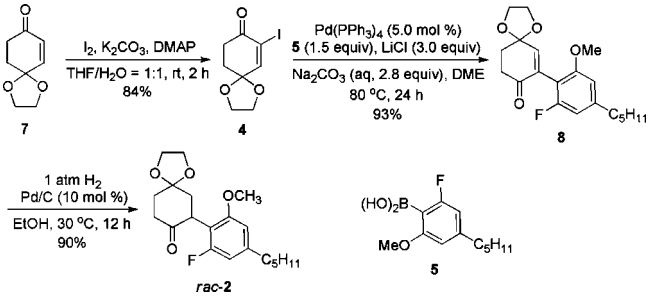
the corresponding chiral alcohols with excellent enantioselectivity and *cis*-selectivity in our previous study.[15] Thus, we introduced a fluorine atom, which has a similar size as hydrogen, to replace one of the methoxy groups of the 2-(2,6-dimethoxyphenyl)cyclohexanone and designed an intramolecular $S_NAr$ cyclization for the construction of a benzopyran ring (Scheme 2).

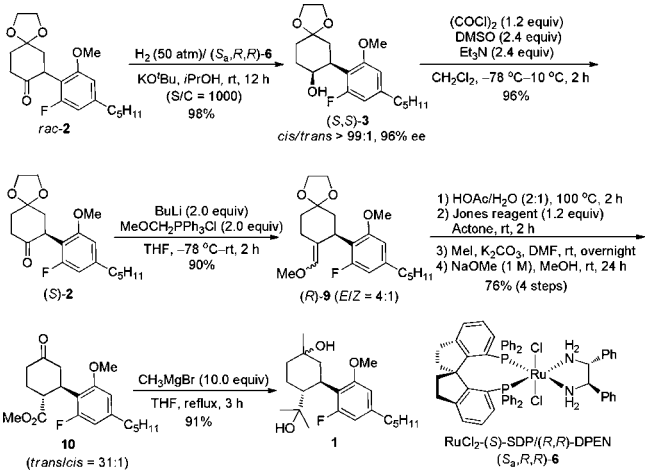
**Scheme 2.** Synthesis of Racemic α-Arylcyclohexanone **2**




The fluorinated α-arylcyclohexanone *rac*-**2** was synthesized from commercially available 1,4-cyclohexenedione monoethylene acetal **7** according to the method we recently developed (Scheme 2).[15] The cyclic enone **7** was iodinated with iodine at room temperature to afford cyclic α-iodoenone **4** in 84% yield. The Suzuki cross-coupling of **4** with arylboronic acid **5**, which was prepared from 3-flouro-5-bromoanisole in two steps including boronation with triisopropyl borate (see Supporting Information), in the presence of 5.0 mol % of $Pd(PPh_3)_4$ as a catalyst and aqueous $Na_2CO_3$ (2.8 equiv) as a base in dimethoxyethane[19] yielded the α-arylated cyclic enone **8** in 93% yield. The enone **8** was hydrogenated on Pd/C (10 mol %) to produce ketone *rac*-**2** in 90% yield.

When the cyclic ketone *rac*-**2** was subjected to the hydrogenation (conditions: S/C = 1000, 50 atm of $H_2$, 0.05 M [KO$^t$Bu], in $^i$PrOH at room temperature) with the catalyst ($S_a$,*R*,*R*)-**6**, we were delighted to find that the hydrogenation completed in 12 h and the desired product, chiral alcohol (*S*,*S*)-**3**, was obtained in 98% yield with 96% ee and >99:1 *cis*/*trans*-selectivity (Scheme 3). The chiral alcohol (*S*,*S*)-**3** was oxidized to ketone (*S*)-**2** in 96% yield by Swern oxidation (conditions: 2.4 equiv of dimethyl sulfoxide, 1.2 equiv of oxalyl chloride, and 2.4 equiv of $Et_3N$). The olefination of (*S*)-**2** with the Wittig reagent, which was generated in situ from $MeOCH_2PPh_3Cl$ (2.0 equiv) and BuLi (2.0 equiv), yielded the olefin (*R*)-**9** in 90% yield (*E*-isomer/*Z*-isomer = 4:1). The olefin (*R*)-**9** was treated with an aqueous AcOH solution at 100 °C for 2 h,[20] followed by an oxidation with the Jones reagent (1.2 equiv) in acetone, esterification with MeI in the presence of $K_2CO_3$ as a base, and isomerization with NaOMe (1 M) in MeOH at room temperature to afford ester **10** in 76% yield (4 steps) with 31:1 *trans*/*cis*-selectivity and 93% ee. A slight loss of ee value possibly occurred in the olefination step of (*S*)-**2** with the Wittig reagent, which involved the use of a strong base. Ester **10** reacted with MeMgBr in refluxing THF for 3 h to provide chiral diol **1** in 91% yield.

**Scheme 3.** Synthesis of Chiral Diol **1**




With enantiomer-enriched diol **1** in hand, we then attempted to construct the benzopyran ring via a base-promoted intramolecular $S_NAr$ cyclization and to complete the enantioselective synthesis of (−)-$\Delta^8$-THC and (−)-$\Delta^9$-THC. The mixture of *cis*- and *trans*-diol **1** was treated with NaH (5.0 equiv) in refluxing DMF for 1 h to yield the tricyclic compound **11** in 94% yield (Scheme 4). Demethylation of **11** by $NaS(CH_2)_2NEt_2$ generated in situ from NaH (10.0 equiv) and $HS(CH_2)_2NEt_2$ (10.0 equiv) afforded the compound **12** in 95% yield. Since the intramolecular $S_NAr$ cyclization and the demethylation reaction proceeded under similar reaction conditions, we attempted to perform these two reactions in one pot. In the presence of 10.0 equiv of NaH and 5.0 equiv of $HS(CH_2)_2NEt_2$ in refluxing DMF, we delightedly obtained the desired compound **12** in high yield (90%). An acid-promoted dehydration of compound **12** in refluxing benzene in the presence of 20 mol % TsOH according to the literature method[3b] produced the target molecule (−)-$\Delta^8$-THC in 96% yield[21] ($[\alpha]_D^{25}$ −163 (*c* 1.0, $CHCl_3$); lit.[10] $[\alpha]_D^{25}$ −152 (*c* 0.46, $CHCl_3$)). When compound **12** was converted to a chlorinated intermediate with the Lucas reagent ($ZnCl_2$/HCl) in acetic acid at room temperature, followed by treatment with potassium *tert*-pentoxide in benzene at 65 °C for 15 min using the same procedure by Petrzilka et al.,[22] the target compound (−)-$\Delta^9$-THC was

(18) The asymmetric hydrogenation of racemic 2-(2,6-dimethoxyphenyl-)cyclohexanone catalyzed by $RuCl_2$((*S*)-SDP)((*R*,*R*)-DPEN) (conditions: S/C = 500, 50 atm $H_2$, room temperature) afforded the desired product in less than 10% yield.

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(20) Petrzilka, M.; Germann, A. *Mol. Cryst. Liq. Cryst.* **1985**, *131*, 327.

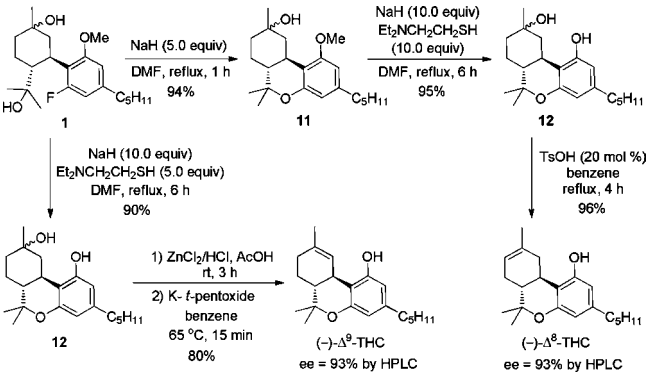
(21) (−)-$\Delta^8$-THC/(−)-$\Delta^9$-THC > 99:1.

(22) Petrzika, T.; Haefliger, W.; Sikemeier, C. *Helv. Chim. Acta* **1969**, *52*, 1102.

(23) (−)-$\Delta^9$-THC/(−)-$\Delta^8$-THC = 97:3. The same results were obtained by using isolated *cis*-**1** or *trans*-**1** as starting material; see Supporting Information.

obtained in 80% yield ($[\alpha]_D^{25}$ −232 (*c* 0.96, $CHCl_3$); lit.[8g] $[\alpha]_D^{25}$ −245 (*c* 0.78, $CHCl_3$)).[23] The NMR spectroscopic data and the optical rotations of our synthetic (−)-$\Delta^8$-THC and (−)-$\Delta^9$-THC are identical to those reported in previous syntheses.

**Scheme 4.** Synthesis of (−)-$\Delta^8$-THC and (−)-$\Delta^9$-THC




In summary, we have developed a new efficient methodology for the enantioselective syntheses of (−)-$\Delta^8$- and (−)-$\Delta^9$-THC. With commercially available 1,4-cyclohexenedione monoethylene acetal **7** as starting material and the ruthenium-catalyzed asymmetric hydrogenation of ketone via DKR and intramolecular $S_NAr$ cyclization as key steps, the optical (−)-$\Delta^8$-THC and (−)-$\Delta^9$-THC were synthesized in 35% and 30% overall yields via 13 and 14 steps, respectively. This synthetic strategy has a high potential for wide application in the synthesis of other biologically active natural products and pharmaceutical agents containing chiral hexahydro-6,6-dimethyl-6*H*-benzo[*c*]chromene motifs.

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**Supporting Information Available.** Experimental procedures and the characterizations of substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.