Natural Product Synthesis | Hot Paper

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# Stereodivergent Total Synthesis of $\Delta^9$-Tetrahydrocannabinols**

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***Abstract:*** *All four stereoisomers of $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC) were synthesized in concise fashion using stereodivergent dual catalysis. Thus, following identical synthetic sequences and applying identical reaction conditions to the same set of starting materials, selective access to the four stereoisomers of THC was achieved in five steps.*

An ongoing challenge in chemical synthesis is the development of efficient transformations that provide rapid and selective access to the full stereochemical array of molecules with multiple stereogenic centers.[1] Such stereodivergent processes have particular potential in natural product syntheses as they can provide both simplified and more direct synthetic pathways to any given stereoisomer of a natural product. Stereodivergent synthesis can also have beneficial impact beyond the realm of synthetic chemistry. The biological properties of an organic compound directly depend on its stereochemical configuration. As such, the ability to access all stereoisomeric permutations of a target molecule allows complete evaluation of stereochemical structure–activity relationships. The preparation of different diastereoisomers of a given natural product or lead candidate traditionally relies on a combination of substrate- and/or catalyst-controlled reactions. Consequently, this results in deviation from the primary synthetic sequence and thus different synthetic routes to the diastereomeric targets.[2] A largely unmet challenge, however, is the discovery and development of uniform synthetic strategies that provide controlled access to any given stereoisomer of a target. Herein, we report the implementation of such a strategy in the context of the total synthesis of the $\Delta^9$-tetrahydrocannabinols (**1**, all stereoisomers) that relies on an early stereodivergent step followed by a short uniform sequence (Figure 1). The two diastereoisomers of $\Delta^9$-tetrahydrocannabinol [$\Delta^9$-THC, (6a*R*,10a*R*)-**1** and (6a*S*,10a*R*)-**1**, Figure 1 a] were isolated from flowering tops of female plants of several *Cannabis sativa* L. varieties.[3] The more abundant (−)-$\Delta^9$-*trans*-THC [(6a*R*,10a*R*)-**1**] is currently used for the treatment of anorexia,[4] as an anti-nauseant for patients undergoing chemotherapy,[5] and for the management of neuropathic pain and spasticity,[6] with side effects including motor impairment and psychosis. Most of the pharmacological effects of this natural product are due to activation of two types of G-protein-coupled receptors, namely the central cannabinoid receptor CB1, which is distributed mainly in the brain, and the peripheral cannabinoid receptor CB2, which is found almost exclusively in the immune system.[7] However, recent studies indicate that some of the effects of THC and other cannabinoids result from a CB1- and CB2-independent mechanism, suggesting that other receptors are involved in the biological response.[8] Such polypharmacology, that is, the activity of a compound at multiple targets, is not uncommon and some antipsychotics are indeed known to bind to more than 20 targets.[9] Our interests in developing a general method for the identification of ligand–receptor interactions and the broad medicinal importance of cannabinoid receptors have led us to develop a uniform synthetic route to the four stereoisomers of $\Delta^9$-THC.[10] Rapid access to any of the four stereoisomers demonstrates the utility of stereodivergent dual catalysis in stereoselective synthesis, and allows investigation of the (poly)pharmacology of all stereoisomers.

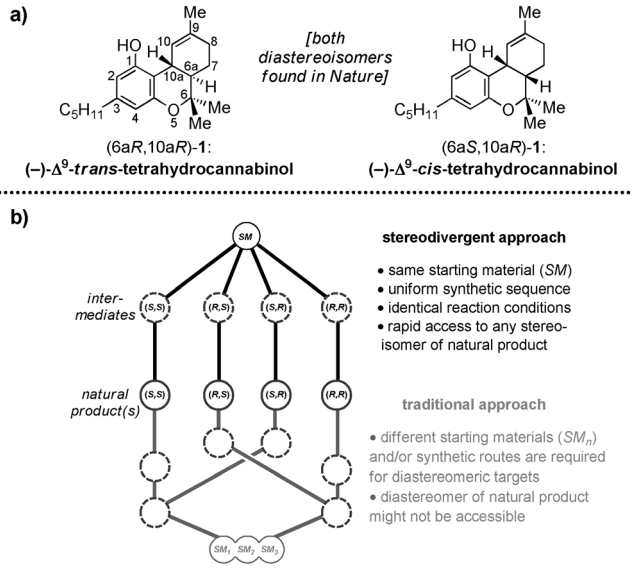


***Figure 1.*** a) Naturally occurring *trans*/*cis* diastereoisomers of $\Delta^9$-tetrahydrocannabinol and b) synthetic roadmaps comparing stereodivergent (in black) with traditional approaches (in gray).

Although $\Delta^9$-*trans*-THC has been prepared several times, only three enantioselective syntheses of the optically pure natural product have been reported to date.[3,11,12] None of these synthetic routes were able to provide access to the diastereoisomeric $\Delta^9$-*cis*-THC as the enantioselectivity-induc-

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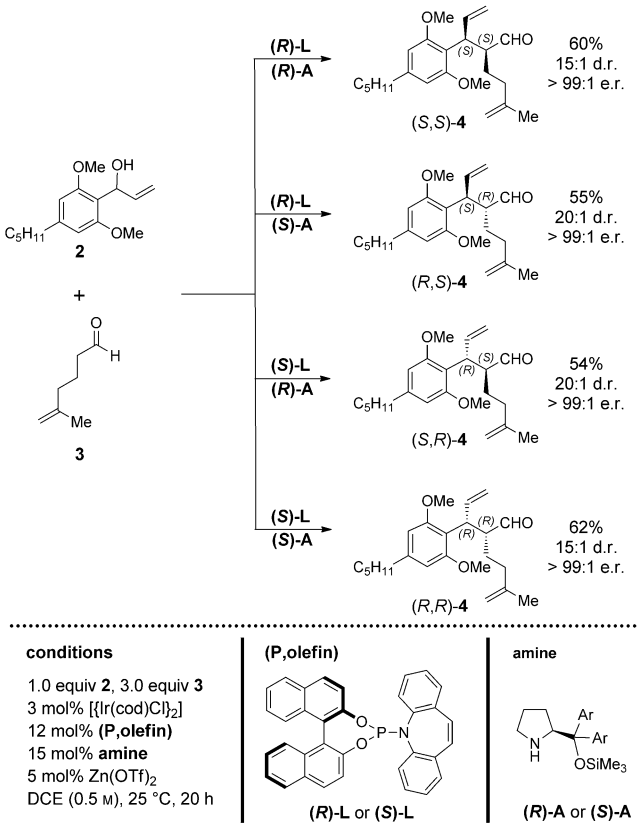
ing step inherently set the configuration of both stereocenters in a single step. As part of our ongoing program on the study of iridium-catalyzed enantioselective transformations,[13] we became interested in their application to the synthesis of complex molecules.[14] We have recently disclosed the concept of stereodivergent dual catalysis[15] as a rational approach to selectively access any given stereoisomer of a molecule bearing two stereocenters.[16] It involves simultaneously using two chiral catalysts, each of which exerts full and independent control over the configuration of one of the centers. To date, the concept has been implemented in the α-allylation of aldehydes catalyzed by a chiral Ir/(P,olefin) complex and a chiral amine. We envisioned expanding this method to provide a general entry into the chiral tetrahydro-6*H*-benzo[*c*]chromene motifs found in many biologically active compounds,[17] including the THCs. Significantly, this process would selectively set the requisite *cis* or *trans* relationship at the cyclohexene ring, a formidable problem associated with the synthesis of these compounds.

The synthesis of all stereoisomers of $\Delta^9$-tetrahydrocannabinol commenced with stereodivergent dual catalytic α-allylation of 5-methylhex-5-enal (**3**) with allylic alcohol **2**[11c] (Scheme 1). Accordingly, a set of two chiral catalysts, an Ir/(P,olefin) complex and a secondary amine, were employed for concurrent activation of allylic alcohol **2** and aldehyde **3**. In the presence of 3 mol% of $[\{Ir(cod)Cl\}_2]$, 12 mol% of **(*R*)-L** or **(*S*)-L**, and 15 mol% of Jørgensen amine **(*R*)-A** or **(*S*)-A**, all possible stereoisomers of γ,δ-unsaturated aldehyde product **4** were obtained in good yields (55–62%) and excellent selectivities (d.r. ≥ 15:1, e.r. > 99:1). A notable difference to our previously disclosed conditions for the α-allylation of linear aldehydes[15b] is the use of $Zn(OTf)_2$ as the promoter. This additive proved to be superior to Brønsted acids as the highly electron-rich allylic alcohol **2** underwent rapid ionization and decomposition in the presence of protic promoters. Importantly, we also noted that epimerization at the C-α center following C–C bond formation was substantially reduced in the presence of $Zn(OTf)_2$, a notable challenge associated with this specific class of products. Finally, this reaction was also conducted on gram scale, affording the stereoisomeric products with comparable yields and selectivities.

With all four stereoisomers of **4** in hand, the synthetic plan called for development of a uniform synthetic sequence that would convert all product isomers into the respective $\Delta^9$-tetrahydrocannabinols. Thus, as depicted in Scheme 2, ring-closing metathesis using Grubbs' second-generation catalyst[18] first secured cyclohexenecarbaldehydes **5** in 85–92% yield. Pinnick oxidation of the aldehydes to the corresponding carboxylic acids, followed by treatment with trimethylsilyldiazomethane gave the corresponding methyl esters **6** (60–66% yield over two steps). This order of chemical events proved to be crucial to obtain **6** in high yields and without noticeable erosion of diastereomeric purity.

To complete the synthesis of the THCs, we designed a one-pot sequence that streamlined conversion of ester **6** into **1** through formation of a tertiary alcohol and double methyl ether deprotection, followed by subsequent intramolecular etherification. Thus, treatment of ester **6** with excess MeMgI




***Scheme 1.*** Stereodivergent preparation of all stereoisomers of **4**. d.r. determined by analysis of the $^1$H NMR spectrum of the unpurified reaction mixture. e.r. of the corresponding primary alcohols determined by supercritical fluid chromatography (SFC) on a chiral stationary phase. Ar = 3,5-$(CF_3)_2$-$C_6H_3$, cod = 1,5-cyclooctadiene, DCE = 1,2-dichloroethane, Tf = trifluoromethanesulfonyl.

at 0 °C to 160 °C at reduced pressure (150 mm Hg) delivered the tertiary alcohol with concomitant removal of the phenolic methyl groups.[19] After aqueous workup and extraction, the organic phase ($CH_2Cl_2$) was treated with $ZnBr_2$, which induced aryl ether formation[20] and furnished $\Delta^9$-THC (**1**, all stereoisomers) in 41–65% yield over the final sequence.

In conclusion, we have developed a fully stereodivergent total synthesis of $\Delta^9$-tetrahydrocannabinols that provides rapid and controlled access to any isomer of the natural product, including the two naturally occurring stereoisomers (−)-$\Delta^9$-*cis*-THC and (−)-$\Delta^9$-*trans*-THC [(6a*S*,10a*R*)-**1** and (6a*R*,10a*R*)-**1**, respectively]. The synthesis relies on a key stereodivergent dual catalytic step that secures any given stereoisomer of γ,δ-unsaturated aldehyde **4** in excellent selectivity from the same set of starting materials under identical conditions. A uniform sequence of four additional steps then completes the synthesis of all stereoisomers of **1**. Additional efforts to gain insight into the biological activity of the unnatural stereoisomers of **1** and to further expand the strategy to other natural products are currently underway in our laboratories and will be reported in due course.

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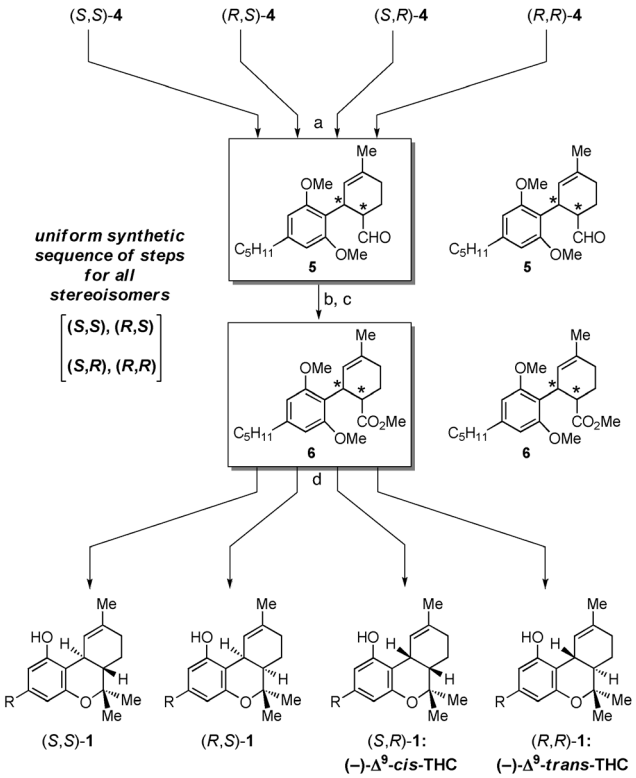


***Scheme 2.*** Stereodivergent preparation of all stereoisomers of $\Delta^9$-THC (**1**). Reagents and conditions: a) Grubbs II cat. (3 mol%), $CH_2Cl_2$, 25 °C, 92% for (*S*,*S*)-**5**, 87% for (*R*,*S*)-**5**, 90% for (*S*,*R*)-**5**, 85% for (*R*,*R*)-**5**; b) $NaClO_2$ (2.3 equiv), $NaH_2PO_4$ (2.0 equiv), 2-methyl-2-butene (30 equiv), *t*BuOH/$H_2O$, 25 °C; c) $Me_3SiCHN_2$ (1.1 equiv), $C_6H_6$/MeOH (1:1), 0 °C, 66% for (*S*,*S*)-**6**, 60% for (*R*,*S*)-**6**, 61% for (*S*,*R*)-**6**, 65% for (*R*,*R*)-**6**; d) MeMgI (10 equiv), $Et_2O$, 0 °C to 160 °C, ambient pressure to 150 mm Hg; then addition of $ZnBr_2$ upon workup in $CH_2Cl_2$, 25 °C, 57% for (*S*,*S*)-**6**, 41% for (*R*,*S*)-**6**, 45% for (*S*,*R*)-**6**, 65% for (*R*,*R*)-**6**. R = $C_5H_{11}$. Atom numbering in the nomenclature of **1** (shown in Figure 1a) has been dropped for clarity; thus, (*S*,*S*)-**1** is (6a*S*,10a*S*)-**1**, and so on.

**Keywords:** dual catalysis · stereodivergent synthesis · tetrahydrocannabinol · total synthesis

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