

## Cationic Bis(oxazoline)Cu(II) Lewis Acid Catalysts. Application to the Asymmetric Synthesis of *ent*- $\Delta^1$ -Tetrahydrocannabinol

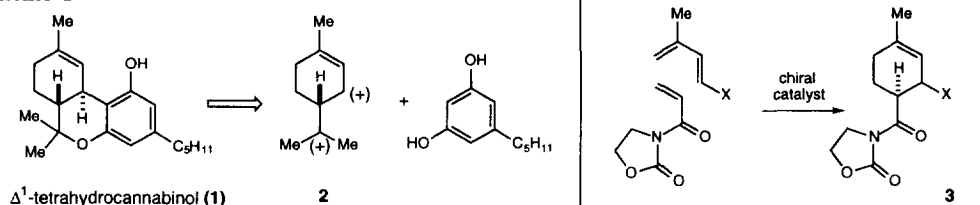
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**Abstract:** The Diels-Alder reaction of acryloyl oxazolidinone and 1-acetoxy-3-methylbutadiene is catalyzed by the cationic bis(oxazoline)Cu(II) complex **4** in high enantioselectivity. The cycloadduct is converted to *ent*- $\Delta^1$ -tetrahydrocannabinol (THC) in four steps. © 1997 Elsevier Science Ltd.

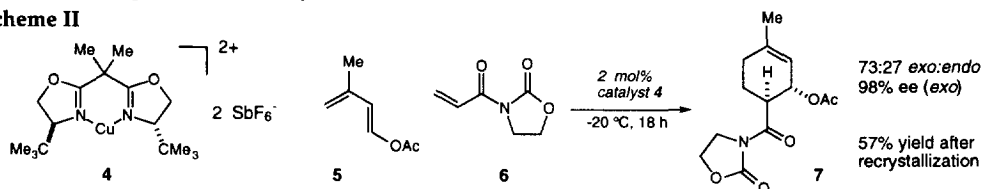
Since the isolation of  $\Delta^1$ -tetrahydrocannabinol ( $\Delta^1$ -THC, **1**) from *Cannabis sativa* in 1964,<sup>1</sup> the potent biological activity of cannabinoids has stimulated the development of a large number of syntheses and allied structure-activity investigations.<sup>2</sup> Previous syntheses of  $\Delta^1$ -THC have utilized the acid-catalyzed condensation of olivetol with monoterpenes, such as (+)-*p*-mentha-2,8-dien-1-ol<sup>3</sup> and (+)-*trans*-2-carene epoxide,<sup>4</sup> each of which functions as an equivalent to the hypothetical dication synthon **2**. In this Letter, we present the first asymmetric synthesis of  $\Delta^1$ -THC, the key step of which is an enantioselective Diels-Alder reaction catalyzed by the cationic bis(oxazoline)Cu(II) complex **4**. This reaction provides cycloadduct **3**, which is equivalent to the dication synthon.

### Scheme I



Previous reports from this laboratory have documented the use of cationic Cu(II) complexes as chiral Lewis acids in the Diels-Alder<sup>5</sup> and aldol addition<sup>6</sup> reactions. In particular, complex **4** (Scheme 2) has been found to be the optimal catalyst for a range of structurally diverse Diels-Alder reactions. The cycloaddition for the present investigation was preceded by the finding that 1-acetoxybutadiene undergoes the analogous reaction with high *endo* selectivity (*cis:trans* = 85:15, *cis ee* = 97%).

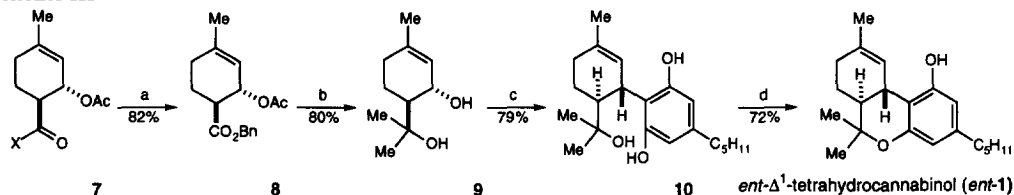
### Scheme II



The Diels-Alder reaction of diene **5** and acrylimide **6** with catalyst **4** (2 mol%,  $\text{CH}_2\text{Cl}_2$ ,  $-20^\circ\text{C}$ , 18 h) afforded cycloadduct **7** as a 73:27 mixture of diastereomers where the major diastereomer, formed with excellent enantioselectivity (98% ee), was isolated by direct crystallization, mp  $124.5^\circ\text{C}$ . Reactions carried out at  $0^\circ\text{C}$  were not as clean, while reactions at temperatures lower than  $-20^\circ\text{C}$  did not exhibit improved

diastereoselectivity. When the reaction was performed on a 50-mmol scale,<sup>8</sup> **7** crystallized out of the unpurified reaction mixture, yielding 57% of enantiomerically and diastereomerically pure material. An X-ray structure of adduct **7** established the *anti* relative stereochemistry of the major diastereomer, formed via an *exo*-transition state. We postulate that a steric interaction between the ligand and the methyl substituent on the diene in the *endo*-transition state accounts for the unanticipated turnover in diastereoselectivity from the corresponding reaction of 1-acetoxybutadiene which is *endo*-selective.

### Scheme III



(a) 2 equiv. LiOBn, THF, -20 °C, 3h. (b) 6 equiv. MeMgBr, ether, 0 °C, 2 h. (c) olivetol, *p*-TSA, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 7h. (d) ZnBr<sub>2</sub>, MgSO<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, 5h.

Imide **7** was cleaved selectively with LiOBn at -20 °C to give **8** in 82% yield (Scheme 3). Addition of methylmagnesium bromide provided diol **9** (80%) which was treated with olivetol and *p*-TSA in CH<sub>2</sub>Cl<sub>2</sub>, in accord with literature precedent,<sup>9</sup> to afford **10** in 79% yield. Finally, the known cyclization of **10** was performed to provide a 72% yield of *ent*-Δ<sup>1</sup>-THC.<sup>9</sup> This procedure delivered *ent*-**1** with no contamination from isomeric THC-related products, which has been reported as a problem in previous syntheses.<sup>3,4</sup> The spectroscopic data of the cyclized product was identical to published data of natural (-)-Δ<sup>1</sup>-THC,<sup>10</sup> with the exception of the rotation, which was opposite in sign: [α]<sub>D</sub><sup>25</sup> (literature) -150 (*c* 0.53, CHCl<sub>3</sub>); [α]<sub>D</sub><sup>25</sup> (synthetic) +141 (*c* 0.55, CHCl<sub>3</sub>). Product absolute configuration is in accord with our previously reported model for asymmetric induction.<sup>5a</sup>

In summary, the highly enantioselective bis(oxazoline)Cu(II)-catalyzed Diels-Alder reaction of imide **6** with 1-acetoxy-3-methylbutadiene provides a useful terpenoid building block. The synthetic utility of **7** has been demonstrated by the asymmetric synthesis of *ent*-Δ<sup>1</sup>-THC in 5 steps from imide **6** in 21% overall yield.

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### References and Footnotes

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- Experimental procedure was followed from ref. 5e. Imide concentration was 0.5 M in CH<sub>2</sub>Cl<sub>2</sub> and three equivalents of diene were used. Yield = 7.56 g (57%). Diastereomer and enantiomer ratios were determined by <sup>1</sup>H NMR and chiral HPLC (Chiracel OD-H, 97:3 hexanes:isopropyl alcohol, 1 ml/min; t<sup>R</sup> (major) = 64 min, 79 min, (minor) = 31 min, 36 min).
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