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

David A. Evans,* Eileen A. Shaughnessy, and David M. Barnes

Department of Chemistry & Chemical Biology, Harvard University, Cambridge, MA 02138, USA

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 1964,¹ the potent biological activity of cannabinoids has stimulated the development of a large number of syntheses and allied structure-activity investigations.² Previous syntheses of $\Delta^1$-THC have utilized the acid-catalyzed condensation of olivetol with monoterpenes, such as (+)-p-mentha-2,8-dien-1-ol³ and (+)-trans-2-carene epoxide,⁴ 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

[Diagram of Δ1-tetrahydrocannabinol (1)]

Scheme II

The Diels-Alder reaction of diene 5⁷ and acrylimide 6 with catalyst 4 (2 mol%, CH₂Cl₂, -20 °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 °C. Reactions carried out at 0 °C were not as clean, while reactions at temperatures lower than -20 °C did not exhibit improved
diastereoselectivity. When the reaction was performed on a 50-mmol scale, 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, CH₂Cl₂, 0 °C, 7h. (d) ZnBr₂, MgSO₄, CH₂Cl₂, 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 CH₂Cl₂, in accord with literature precedent, to afford 10 in 79% yield. Finally, the known cyclization of 10 was performed to provide a 72% yield of ent-Δ1-THC. This procedure delivered ent-1 with no contamination from isomeric THC-related products, which has been reported as a problem in previous syntheses. The spectroscopic data of the cyclized product was identical to published data of natural (-)-Δ1-THC, with the exception of the rotation, which was opposite in sign: [α]D²⁵ (literature) -150 (c 0.53, CHCl₃); [α]D²⁵ (synthetic) +141 (c 0.55, CHCl₃). Product absolute configuration is in accord with our previously reported model for asymmetric induction.

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-Δ1-THC in 5 steps from imide 6 in 21% overall yield.

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References and Footnotes

7) (a) Bailey, W. J.; Barclay, R. J. Org. Chem. 1955, 21, 326-331. Attempts to form the diene through the rearrangement of 2-methylbut-3-yn-2-ol with Ag(I) and acetic anhydride resulted in the formation of a mixture of products which were difficult to separate. See: (b) Banks, R. E.; Miller, J. A.; Nunn, M. J.; Stanley, P.; Weakley, T. J.; Ullah, Z. J. Chem. Soc., Perkin Trans. I 1981, 1096-1102. (c) Snider, B. B.; Amin S. G. Synth. Comm. 1978, 8, 117.
8) Experimental procedure was followed from ref. 5e. Imide concentration was 0.5 M in CH₂Cl₂ and three equivalents of diene were used. Yield = 7.56 g (57%). Diastereomer and enantiomer ratios were determined by 1H NMR and chiral HPLC (Chiracel OD-H, 97:3 hexanes/isopropyl alcohol, 1 mL/min; [α]D (major) = 64 min, 79 min, (minor) = 31 min, 36 min). 
9) Stoss, P.; Marrath, P. Synlett 1991, 553-554. Reaction at low concentration (0.003 M) minimized the formation of by-products.

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