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

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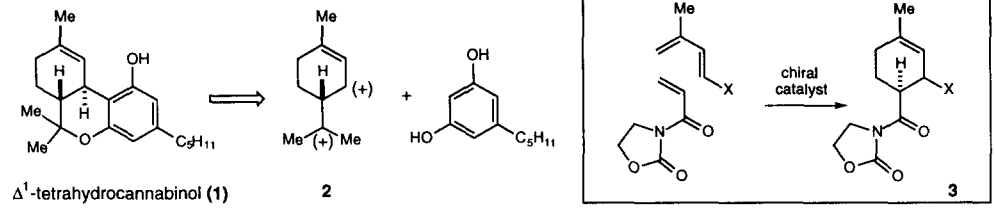
Abstract: The Diels-Alder reaction of acryloyl oxazolidinone and 1-acetoxy-3-methylbutadiene is catalyzed by the cationic bis(oxazoline)Cu(II) complex **4** in high enantioselectivity. The cycloadduct is converted to *ent*-Δ^1-tetrahydrocannabinol (THC) in four steps. © 1997 Elsevier Science Ltd.

Since the isolation of Δ^1-tetrahydrocannabinol (Δ^1-THC, **1**) from *Cannabis sativa* in 1964,[1] the potent biological activity of cannabinols has stimulated the development of a large number of syntheses and allied structure-activity investigations.[2] Previous syntheses of Δ^1-THC have utilized the acid-catalyzed condensation of olivetol with monoterpenes, such as (+)-*p*-mentha-2,8-dien-1-ol[3] 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 Δ^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.

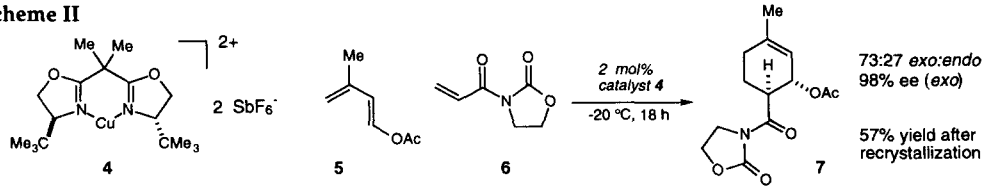
Scheme I



Δ^1-tetrahydrocannabinol (**1**) **2**

Previous reports from this laboratory have documented the use of cationic Cu(II) complexes as chiral Lewis acids in the Diels-Alder[5] and aldol addition[6] 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 precedented by the finding that 1-acetoxybutadiene undergoes the analogous reaction with high *endo* selectivity (*cis*:*trans* = 85:15, *cis* ee = 97%).

Scheme II

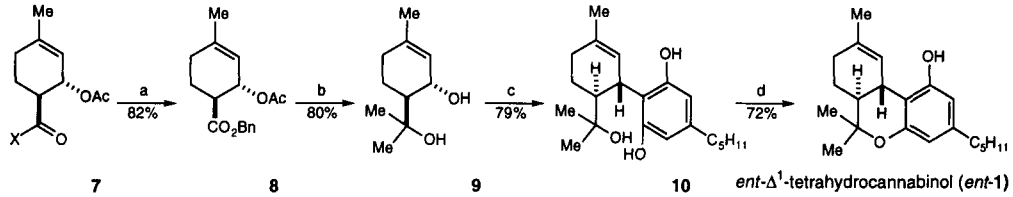


4 **5** **6** **7**

The Diels-Alder reaction of diene **5**[7] and acrylimide **6** with catalyst **4** (2 mol%, CH_2Cl_2, -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,[8] **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_2Cl_2, 0 °C, 7h. (d) $ZnBr_2$, $MgSO_4$, CH_2Cl_2, 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_2Cl_2, in accord with literature precedent,[9] to afford **10** in 79% yield. Finally, the known cyclization of **10** was performed to provide a 72% yield of *ent*-Δ^1-THC.[9] This procedure delivered *ent*-**1** with no contamination from isomeric THC-related products, which has been reported as a problem in previous syntheses.[3,4] The spectroscopic data of the cyclized product was identical to published data of natural (-)-Δ^1-THC,[10] with the exception of the rotation, which was opposite in sign: $[\alpha]_D^{25}$ (literature) -150 (*c* 0.53, $CHCl_3$); $[\alpha]_D^{25}$ (synthetic) +141 (*c* 0.55, $CHCl_3$). Product absolute configuration is in accord with our previously reported model for asymmetric induction.[5a]

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^1-THC in 5 steps from imide **6** in 21% overall yield.

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References and Footnotes

1) Gaoni, Y.; Mechoulam, R. *J. Am. Chem. Soc.* **1964**, *86*, 1646-1647.
2) Mechoulam, R.; McCallum, N. K.; Burstein, S. *Chem. Rev.* **1976**, *76*, 75-112.
3) Razdan, R. K.; Dalzell, H. C.; Handrick, G. R. *J. Am. Chem. Soc.* **1974**, *96*, 5860-5865.
4) Crombie, L.; Crombie, W. M. L.; Jamieson, S. V.; Palmer, C. J. *J. Chem Soc., Perkin Trans. I* **1988**, 1243-1250.
5) (a) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, 115, 6460-6461. (b) Evans, D. A.; Lectka, T.; Miller, S. J. *Tetrahedron Lett.* **1993**, 34, 7027-7030. (c) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798-800. (d) Evans, D. A.; Kozlowski, M. C.; Tedrow, J. S. *Tetrahedron Lett.* **1996**, *37*, 7481-7484. (e) Evans, D. A.; Barnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 57-58.
6) (a) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814-5815. (b) Ref. 6d.
7) (a)Bailey, W. J.; Barclay, R. *J. Org. Chem.* **1955**, *21*, 328-331. 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 CH_2Cl_2 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; t^R (major) = 64 min, 79 min, (minor) = 31 min, 36 min).
9) Stoss, P.; Merrath, P. *Synlett* **1991**, 553-554. Reaction at low concentration (0.003 M) minimized the formation of by-products.
10) (a) Petrzilka, T.; Haefliger, W.; Sikemeier, C. *Helv. Chim. Acta* **1969**, 1102. (b) Archer, R. A.; Johnson, D. W.; Hagaman, E. W.; Moreno, L. N.; Wenkert, E. *J. Org. Chem.* **1977**, *42*, 490-495.

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