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The First Enantioselective Synthesis of the Chemotactic Factor Sirenin by an Intramolecular [2 + 1] Cyclization Using a New Chiral Catalyst

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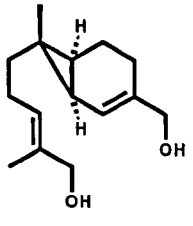
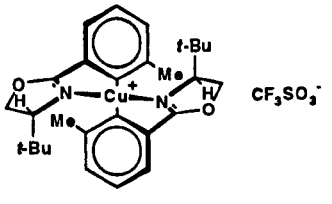
Summary: A simple, highly enantioselective synthesis of sirenin (1) (bioactive form) has been developed which depends on the intramolecular [2 +1] cycloaddition reaction of diazo ester 5 to form bicyclic ester 6 (95 : 5 enantioselectivity) using a new and remarkably stable monomeric chiral Cu(I) complex (2) whose structure was proven by X-ray diffraction analysis.

Sirenin (**1**) is a remarkably potent sperm attractant of the water mold *Allomyces*[1,2] which has been a synthetic target for several groups. Although there have been a number of syntheses of racemic **1**,[3] and one synthesis of the enantiomers of **1** via racemic intermediates with resolution,[4] to date there has not been an enantioselective synthesis, i.e. specific for the natural form of sirenin. In this paper we report a short and efficient catalytic enantioselective synthesis of enantiomerically pure sirenin in the natural levorotatory form. The initial synthetic investigations were concerned with the evaluation of known chiral Cu(I) and Rh(II) catalysts for [2 + 1] cycloaddition to form the cyclopropane ring system. Since none of these reagents afforded acceptable levels of enantioselection, we turned to the development of other catalysts. These studies have led to a new Cu(I) based catalytic system (**2**) which proved to be a superior reagent for the synthesis of **1** and which is potentially more broadly useful in synthesis.

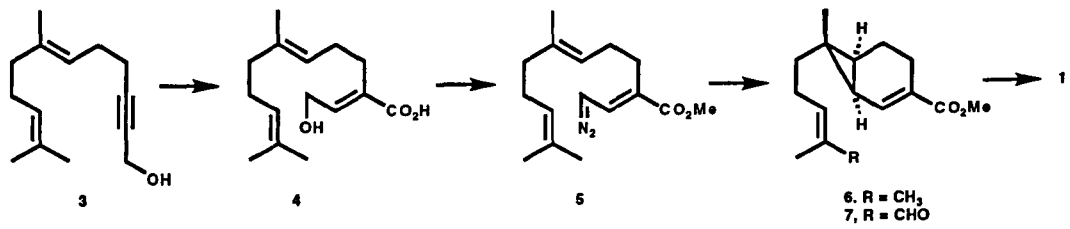


1



2

The propargylic alcohol **3** was treated with 2 equiv of $Ni(CO)_4$ in 25 : 3 : 6 EtOH–AcOH–H_2O at 70 °C for 50 min, cooled to 0 °C and stirred with 0.5 vol of 5% H_2SO_4 and 3 vol of ether for 25 min to give after extractive isolation and chromatography on silica gel the hydroxy acid **4** in 64% yield.[3c] This hydroxy acid was esterified (CH_2N_2 in Et_2O, 92%) and oxidized to the corresponding α,β-unsaturated aldehyde (MnO_2, hexane, 0°, 20 min) which was transformed into the diazo ester **5** by the sequence: (1) hydrazone formation (NH_2NH_2 in EtOH at 23 °C for 2 h) and (2) oxidation (MnO_2, CH_2Cl_2, 0 °C, 2 h) (77% overall yield).[3c] The diazo ester **5** was stirred with 2 mol % of the (*R,R,R*)-catalyst **2** in CH_2Cl_2 solution at 0 °C for 3 h to afford cleanly the bicyclic ester **6** of 90% ee, as determined by HPLC analysis (254 nm) using a Chiralcel OD column with 0.25% *i*-PrOH in hexane as eluant at 23 °C.[5] Purification of **6** from the reaction mixture by chromatography on a preparative Chiralcel OD column (2 cm diam) afforded enantiomerically pure **6** in 77% yield based on **5**. Oxidation of **6** (SeO_2, EtOH at reflux for 13 h) provided the aldehyde ester **7** (58%) which upon reduction ($LiAlH_4$, $AlCl_3$, Et_2O at -10 °C for 1.5 h) produced in 91% yield sirenin, $[\alpha]_D^{23}$ -48° (c=0.8, $CHCl_3$); lit.[1] $[\alpha]_D^{22}$ -45° (c=1.0, $CHCl_3$), which was spectroscopically identical with authentic material.



The key to the realization of the highly enantioselective synthesis of the bioactive form of sirenin (**1**) described above was the development of the new Cu(I) catalyst **2**. The experimental and conceptual steps which led to the discovery of this new and potentially widely useful system will now be outlined. First of all, we surveyed each of the promising known catalysts for enantioselective [2 + 1] carbenoid-olefin addition for their effectiveness in the enantioselective transformation of **5** to **6**. Shown below (Figure 1) are the results for each catalyst as % ee under optimal conditions at 0° to 23 °C for the product **6** or *ent*-**6**. The structures shown for the Masamune-Evans bisoxazoline type catalysts are hypothetical since X-ray crystallographic analysis of the complex R=*t*-Bu revealed a non-chelate helical polymeric structure in the solid state.[8] However, NMR analysis of solutions of these Cu(I) catalysts is consistent with less aggregated structures, the precise nature of which are not now known.[8] The unexpectedly poor results obtained for the conversion **5** → **6** with the known Cu(I) bisoxazoline complexes suggested that catalysis by aggregated species might compete with that by the 1 : 1 chelate structure and that Cu(I) complexes with ligands which allow a larger L–Cu–L angle in the chelate ring (between 120 and 180°) might be completely monomeric and much more effective. Accordingly, the (*R,R,R*) ligand **8** of complex **2** was synthesized as outlined in Figure 2. The enantiomeric (*S,S,S*) ligand **9** was prepared similarly.[9,10] Treatment of **8** with 1 equiv of CuOTf • 0.5 C_6H_6 in CH_2Cl_2 with stirring at 23 °C for 2 h, filtration, removal of solvent and recrystallization from 1,2-dichloroethane-2,2,4-trimethylpentane afforded the 1 : 1 complex **2** as colorless crystals: mp 275-276 °C; (*S,S,S*): $[\alpha]_D^{23}$ -68° (c = 1.38, CH_2Cl_2); (*R,R,R*): $[\alpha]_D^{23}$ +68° (c = 1.38, CH_2Cl_2).

The structure of (*S,S,S*)-**2** was determined by X-ray crystallographic analysis, the results of which are summarized in formula **10** below.[11] The Cu(I) center is contained in a 9-membered chelate ring and is coordinated with one of the triflate oxygens in the solid state; the N–Cu–N angle was determined to be 134°. This complex is surprisingly stable in air either in the solid state or in solution, in contrast to the Masamune-Evans

Figure 1. Enantioselection (% ee) for **5** → **6** or *ent*-**6**.

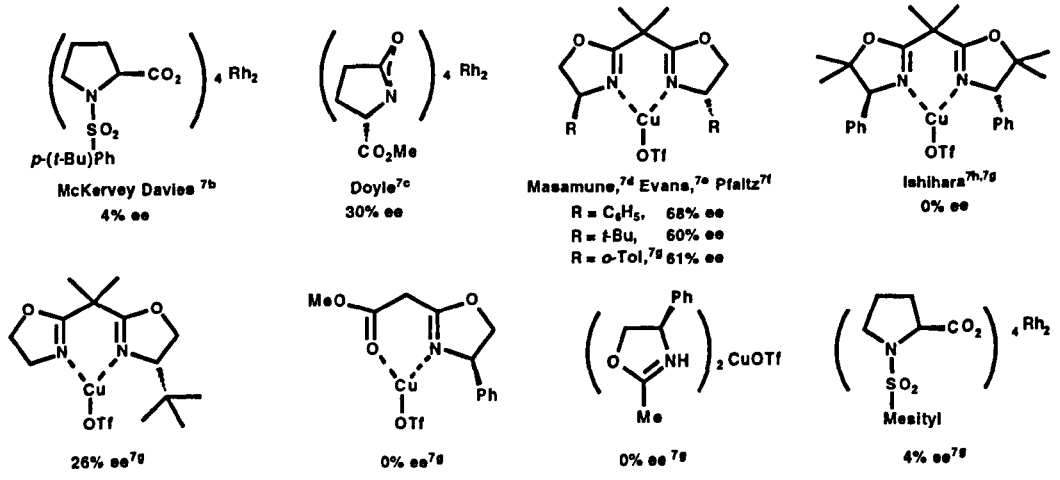
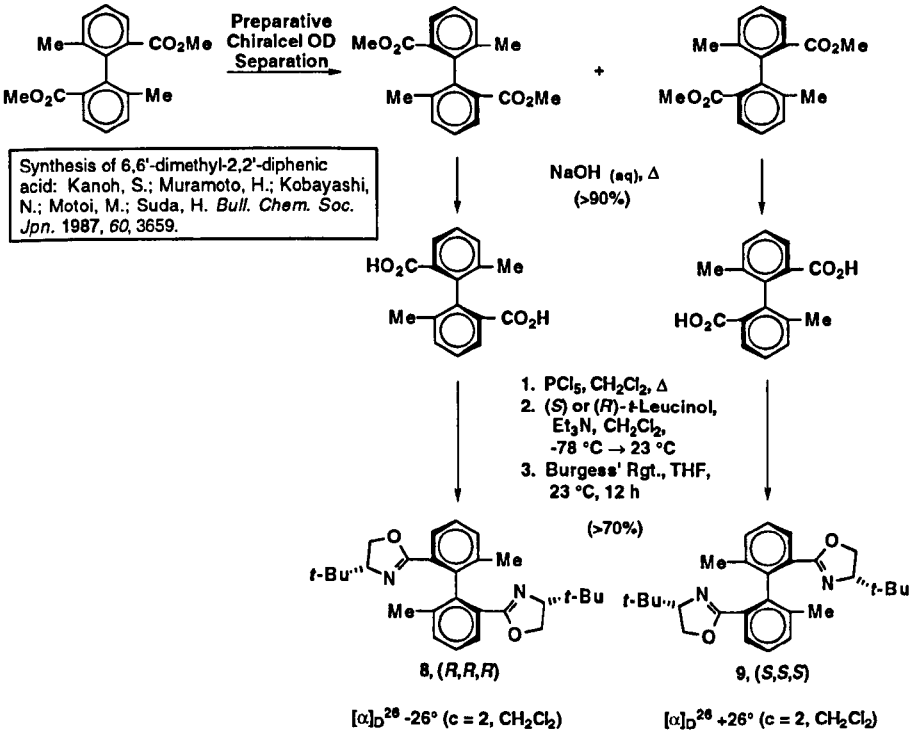
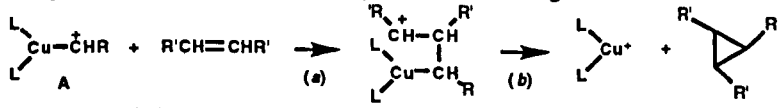


Figure 2. Synthesis of ligands 8 and 9.

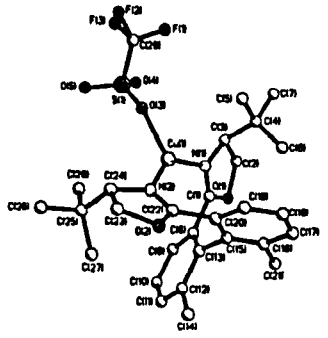


complexes which are very air-sensitive in solution. It is evident that the 9-membered ring and the 134° N–Cu–N angle are important to the unusual stability and that this monomeric structure as the triflate ion pair is the catalytically active species. Although the precise mechanism of the catalytic intramolecular cyclopropanation reaction has not yet been experimentally demonstrated, it seems reasonable to assume the intermediacy of a Cu(I)-carbenoid (which can be formulated as A). One possible pathway from such an intermediate is as follows. Steps (*a*) and (*b*) may be separate in time or, more likely, synchronous (leading to a concerted [2 + 1] cycloaddition

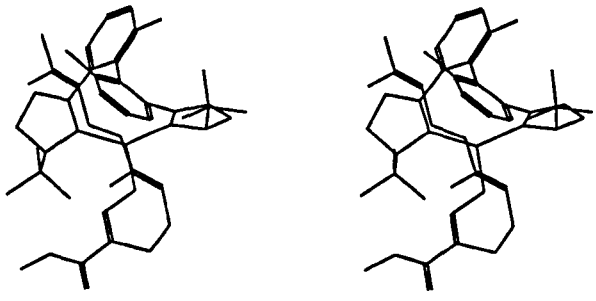


process from A). This mechanistic pathway is consistent with the observed absolute stereochemical course of the reaction of **2** and **5** to form **6**. A plausible transition-state assembly for this enantioselective reaction is shown by stereopair **11**.[12] The corresponding (diastereomeric) transition state leading from **2** and **5** to *ent*-**6** is relatively unfavorable due to non-bonded steric repulsions involving the substrate and one of the *t*-butyl groups of the catalyst.

Catalyst **2** and its enantiomer are readily synthesized and remarkably stable, even in solution in the presence of air, and the corresponding ligands **8** and **9** are also stable and readily recoverable. We expect that there are many possible useful applications of these and related compounds and such studies are underway. The (*R*,*S*,*R*)-and (*S*,*R*,*S*) diastereomers have also been synthesized and studied, and have been converted to Cu(I) complexes. However, as expected from the mechanistic considerations described above and from inspection of accurate scale models, these complexes provide only mediocre levels of enantioselectivity in the transformation of **5** to **6**.



10 (X-ray, *S,S,S*-**2**) (*ent*-**2**)



11 (stereopair from *R,R,R*-**2**)

In conclusion we emphasize that catalyst **2** and its structural analogs are very promising new catalytic species, as is suggested by the efficient synthesis of **1** which is detailed herein.[13]

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5. The retention times on this Chiralcel OD column at a flow rate of 0.8 mL/min were 9.9 min for **6** (configuration corresponding to sirenin) and 11.7 min for the enantiomer of **6** (ratio **6** : *ent*-**6** ca. 20 : 1).
6. The following rotations were measured for chiral intermediates: for **6**, $[\alpha]_D^{23}$ +61° (c=1.8, $CHCl_3$); for **7**, $[\alpha]_D^{23}$ +48° (c=1, $CHCl_3$).
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10. (a) For a recent review of oxazolines, see Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297. (b) For syntheses and applications of bis-oxazolines of biaryls, see Nelson, T. D.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 2577 and Rawson, D.; Meyers, A. I. *J. Chem. Soc., Chem. Commun.* **1992**, 494.
11. (a) Detailed X-ray crystallographic data for *ent*-**2** are obtainable from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K. (b) Empirical formula of *ent*-**2**, $C_{29}H_{36}CuF_3N_2O_5S$; monoclinic; space group P2(1); a = 12.764(2) Å, b = 15.147(4) Å, c = 16.276(3) Å; β = 92.560(10)°; V = 3143.6(11) $Å^3$, Z = 4; M_o–K_α radiation (23 °C); reflections collected 6673, unique reflections 6037; refinement method: full-matrix, least squares of F^2; GOF on F^2 = 1.05; final R indices [I>2 sigma (I)]; R_1 = 0.0744, wR_2 = 0.1878. Cu–ligand bond lengths: Cu–N = 1.925(13), Cu–O(3) = 2.072(13); < N(1)CuN(2) = 134°.
12. A [2 + 2] Cu–carbenoid–olefin cycloaddition mechanism is also a formal possibility which must remain under consideration. One problematic aspect of this pathway, at least for the transformation of **5** to **6** in the present study, is the apparent large degree of steric repulsion involved in the [2 + 2] cycloaddition step.

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