of this fully conjugated intermediate in addition to introduction of an active site base is likely to be crucial in successful antibody catalysis of the proton transfer. Such an active site base might be introduced either by hapten design or by attaching a base to the cofactor.[11]

Antibody-cofactor catalysis of enantioselective amino acid synthesis remains an attractive goal. This study demonstrates the feasibility of the initial step of PLP catalysis: stereospecific formation of an aldimine intermediate. Improvements in hapten design coupled with mutagenesis or genetic selections may yield antibodies with the desired catalytic capabilities.

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Supplementary Material Available: Experimental details for the preparation of **1-11**, kinetic assays, and determination of antibody-inhibitor dissociation constants (11 pages). Ordering information is given on any current masthead page.

Chiral Dihydropyridones as Synthetic Intermediates. Asymmetric Synthesis of (+)-Elaeokanine A and (+)-Elaeokanine C

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Since their isolation by Jones and co-workers,[1] the *Elaeocarpus* alkaloids have received considerable attention as targets for synthesis. Elaeokanine A (**1**) has been prepared several times in racemic form[2] and once enantioselectively.[3] The synthesis of (±)-elaeokanine C (**2**) has also been carried out in several laboratories,[4] but an enantioselective preparation has not been previously reported and the absolute configuration of the natural product was unknown. As part of a program directed at developing the utility of 1-acyldihydropyridines and 1-acyldihydropyridones as synthetic intermediates,[5] we explored a strategy for the enantioselective synthesis of the elaeokanines A and C that was based on our recently developed asymmetric synthesis of 2-alkyl-2,3-dihydro-4-pyridones.[6] Our synthetic plan followed the retrosynthetic analysis shown in Figure 1.

Reaction of chiral 1-acylpyridinium salt **3**, prepared in situ from 4-methoxy-3-(triisopropylsilyl)pyridine[6] and the chloroformate of (-)-8-(4-phenoxyphenyl)menthol,[7] with Grignard reagent **4**[8]

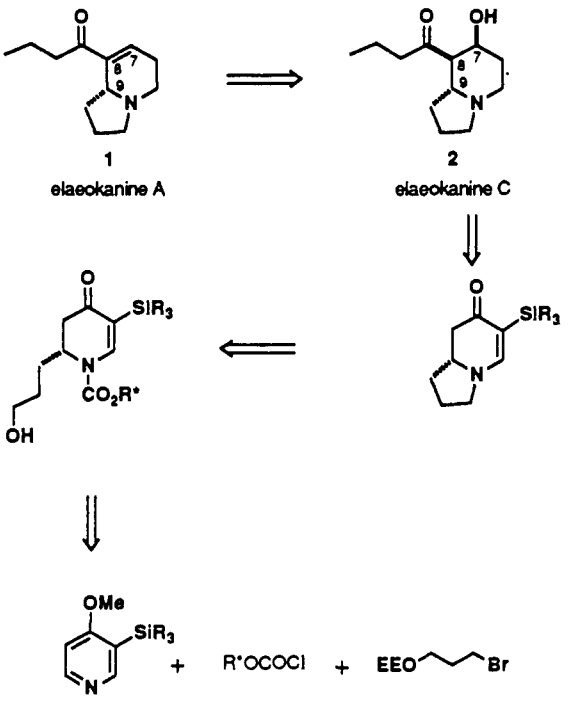
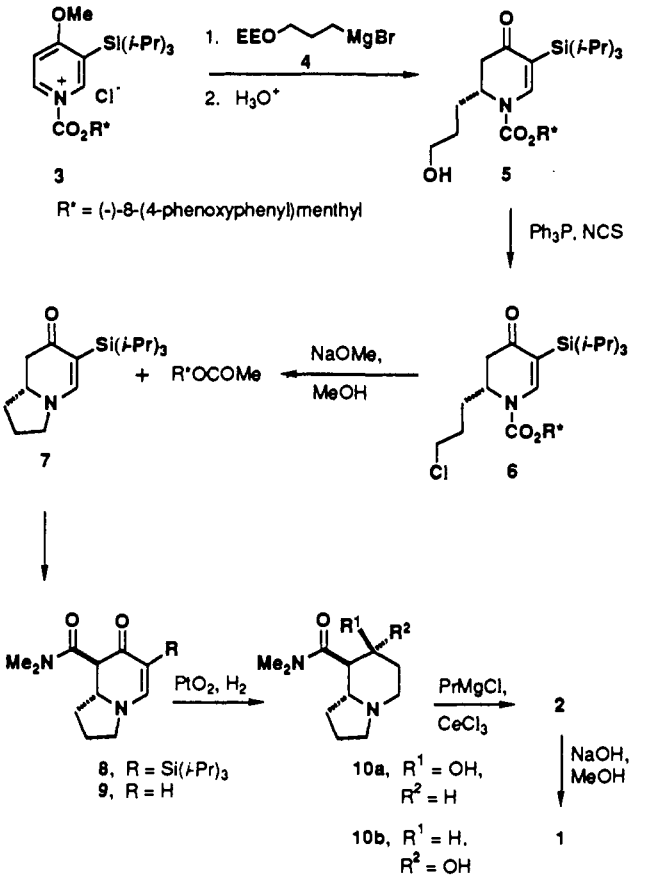


Figure 1.

in THF/toluene at -78 °C gave the alcohol **5** in 82% crude yield and 94% de. After purification by chromatography (silica gel, 10% EtOAc/hexane), alcohol **5** (65% yield) was converted to chloride **6**, mp 81-83 °C, in 89% yield by treatment with triphenylphosphine and *N*-chlorosuccinimide.[9] On removal of the



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chiral auxiliary with sodium methoxide in methanol[6] (4 equiv, reflux, 2.5 h), *concomitant cyclization occurred to give enone 7 from 6 in 84% yield.* The chiral auxiliary was recovered as its methyl carbonate in 94% yield. Treatment of **7** [mp 90–91 °C; $[\alpha]^{23}_D$ +535° (*c* 0.89, $CHCl_3$)] with LDA (2 equiv, THF, −78 °C) and dimethylcarbamyl chloride (4 equiv) gave a 92% yield of amide **8**, mp 136–138 °C, and the corresponding cis diastereomer in a ratio of 97:3. The triisopropylsilyl (TIPS) group of **8** was removed with oxalic acid in methanol to provide **9** [mp 122–124 °C; $[\alpha]^{23}_D$ +1072° (*c* 1.1, $CHCl_3$)] in 96% yield. The enantiomeric purity of **9** was determined to be >98% by chiral column GC analysis.[10] The next step of the synthesis required a stereoselective reduction of the enaminone moiety of **9** to give amino alcohol **10a**. This was accomplished in one step using catalytic hydrogenation over washed[11] PtO_2. In this manner a 95:5 mixture of **10a** and **10b** was obtained in 96% yield. The last step of our elaeokanine C synthesis called for converting the *N,N*-dimethylamide group of **10a** to an *n*-propyl ketone. Although organocerium reagents are known to convert amides to ketones,[12] no examples of the analogous conversion with β-hydroxy amides were reported. Treatment of **10a** with anhydrous cerium chloride (2.5 equiv) and *n*-propylmagnesium chloride (3 equiv, 0 °C, 4 h) gave a 66% yield of elaeokanine C (**2**) [$[\alpha]^{23}_D$ +47° (*c* 0.4, $CHCl_3$)]. In the absence of cerium chloride, the analogous reaction gave only recovered starting material. Our synthetic **2** was determined to be >95% optically pure by chiral column GC analysis.[10] The literature optical rotation value for natural elaeokanine C is $[\alpha]_D$ −14° (*c* 1.0, $CHCl_3$).[1] On the basis of the literature rotation value and the work described in this communication, the isolated *natural* (−)-elaeokanine C was only 29% optically pure, with the major enantiomer having the absolute configuration 7*R*,8*S*,9*S*.[13] Treatment of (+)-elaeokanine C (**2**) with NaOH/MeOH[2e] gave (+)-elaeokanine A (**1**) in 30% yield;[14] $[\alpha]^{23}_D$ +47° (*c* 0.31, $CHCl_3$) [lit.[1] $[\alpha]_D$ +13° (*c* 0.9, $CHCl_3$); lit.[3] $[\alpha]^{22}_D$ +49° (*c* 0.5, $CHCl_3$)].

Interestingly, application of our dihydropyridone asymmetric synthesis in the above syntheses led to the enantioselective preparation of natural (+)-elaeokanine A and unnatural (+)-elaeokanine C. We have determined that these two closely related alkaloids have *opposite* absolute stereochemistry at C-9 of their indolizidine ring system. Our enantioselective synthesis[15] of (+)-elaeokanine C was accomplished with a high degree of regio- and stereocontrol in seven steps from readily available 4-methoxy-3-(triisopropylsilyl)pyridine. This approach to alkaloid synthesis is attractive from a practical standpoint as the chiral auxiliary is introduced in situ, removed during the cyclization step, and easily recovered in high yield. This synthesis clearly demonstrates the potential of enantiopure dihydropyridones as chiral building blocks. The syntheses of (−)-elaeokanine C and other naturally occurring *Elaeocarpus* alkaloids are under investigation and will be reported in due course.

Acknowledgment. We gratefully acknowledge support of this work by the National Institutes of Health (Grant GM 34442).

Supplementary Material Available: Listings giving full spectroscopic and analytical characterization of **2**, **5–9**, and **10a** (7 pages). Ordering information is given on any current masthead page.

(10) The enantiomeric purity was determined by capillary gas chromatography using a Chirasil-Val column (Alltech Associates, Inc., Deerfield, IL). A derivative of alcohol **2** was prepared prior to GC analysis; see: Kōnig, W.; Francke, W.; Benecke, I. *J. Chromatogr.* **1982**, *239*, 227.

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(13) Structure **2** is depicted with the absolute stereochemistry found in our synthetic (+)-elaeokanine C.

(14) The spectral properties of (+)-**1** were identical with those reported.[2]

(15) All new compounds were spectroscopically characterized and furnished satisfactory elemental analyses (C,H,N ±0.4%) or high-resolution mass spectra. Details are provided in the supplementary material.

Reduction and Chain Extension of the Carbene Ligand of Rhenium Carbene Complexes

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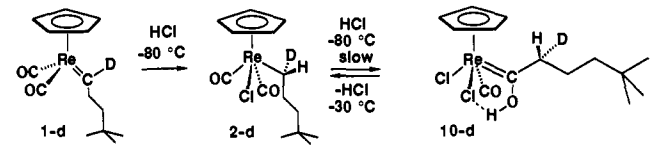
Recently we reported that stereospecific addition of HCl to the amphiphilic carbene complex $C_5H_5(CO)_2Re{=}CDCH_2CH_2CMe_3$ (**1-*d***) produced the alkylchlororhenium complex *cis*-$C_5H_5(CO)_2ClReCHDCH_2CH_2CMe_3$ (**2-*d***).[1] Upon warming to −13 °C for 2 h, the initially formed diastereomer of **2** rearranged to a 1:1 mixture of the two possible diastereomers of **2**. Upon further warming to room temperature, **2** lost HCl to form the rhenium–alkene complex $C_5H_5(CO)_2Re(CHD{=}CHCH_2CMe_3)$ (**3-*d***). Possible mechanisms that we considered for interconversion of the diastereomers of **2-*d*** included (1) reversible, partially nonstereospecific loss of HCl from **2-*d*** to reform carbene complex **1-*d***, (2) intramolecular rearrangement of **2-*d*** via a pseudorotation process, and (3) ionization of halide.



In the course of studying the possible reversible loss of HCl from **2**, we looked for exchange of deuterium from **2-*d*** with excess HCl. No loss of deuterium label was observed, but we noted the formation of a single new species whose ^1H NMR spectrum was too complex to be readily assigned.

Concurrent studies of the reaction of HCl with the related carbene complex $C_5Me_5(CO)_2Re{=}CHCH_3$ (**4**) clarified the situation. Here we report that reaction of **4** with excess HCl leads to reduction and chain extension of the carbene ligand and formation of the hydroxycarbene complex *cis*-$C_5Me_5(CO)Cl_2Re{=}C(OH)CH_2CH_3$ (**5**).

Rhenium carbene complex **4** was prepared by a route similar to that employed in the preparation of **1**;[2] reaction of $Cp_2Zr(\eta^2\text{-}COCH_3)Cl$ with $C_5Me_5(CO)_2ReH^-K^+$ led to the isolation of $C_5Me_5(CO)_2Re{=}CHCH_3$ (**4**)[3] in 84% yield. Reaction of **4** with 2 equiv of HCl in pentane at −80 °C, followed by workup at 0 °C, led to the formation of *cis*-$C_5Me_5(CO)_2ClReCH_2CH_3$ (**6**)[3] in 80% yield. Reaction of either **4** or **6** with excess HCl in CD_2Cl_2 at −80 °C led to the formation of a single new species, which was characterized spectroscopically at low temperature as the hydroxycarbene complex *cis*-$C_5Me_5(CO)Cl_2Re{=}C(OH)CH_2CH_3$ (**5**).[3] The ^{13}C NMR spectrum of **5** exhibited a 1:1 intensity ratio of peaks due to a CO ligand at δ 213.6 and a carbene ligand at δ 283.2. The IR spectrum of **5** in CH_2Cl_2 at −80 °C had a single carbonyl band at 1964 cm^{-1} and a broad weak absorption in the region >3000 cm^{-1} possibly due to the hydroxyl group. In the ^1H NMR spectrum of **5**, a far downfield doublet at δ 14.34 (J = 1.4 Hz) was assigned to a hydroxyl proton coupled to a single diastereotopic methylene proton of the ethyl side chain.[4] Treatment of a CD_2Cl_2 solution of **5** with excess CH_3OD washed out the doublet at δ 14.34. The presence of an intramolecular hydrogen bond between chlorine and the OH group is consistent with the far downfield ^1H NMR chemical shift of the OH signal

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(3) See the supplementary material for experimental details and full characterization.

(4) *cis*-$(CO)_4BrMn{=}C(OH)CH_3$,[4a] *cis*-$(CO)_4BrRe{=}C(OH)CH_3$,[4b] and $(PPh_3)_2(CO)(N_2)ClRe{=}C(OH)CH_3$[4c] are three examples of hydroxycarbene metal halides, having intramolecular hydrogen bonds, that were prepared by addition of organolithium reagents to metal carbonyl halides. (a) Moss, J. R.; Green, M.; Stone, F. G. A. *J. Chem. Soc., Dalton Trans.* **1973**, 975. (b) Darst, K. P.; Lukehart, C. M. *J. Organomet. Chem.* **1979**, *171*, 65. (c) Chatt, J.; Leigh, G. J.; Pickett, C. J.; Stanley, D. R. *J. Organomet. Chem.* **1980**, *184*, C64.

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