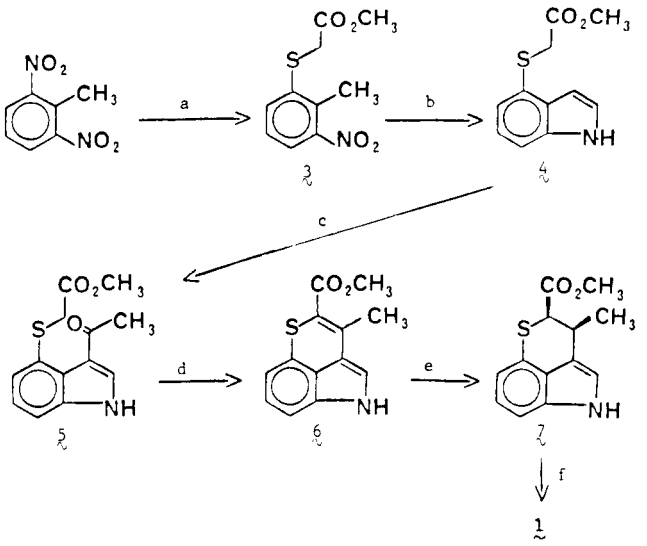
Scheme II. Synthesis of (±)-Chuangxinmycin[a]



[a] (a) $HSCH_2CO_2CH_3$, HMPA, LiOH, room temperature. (b) (i) KOH, MeOH; (ii) $(CH_3)_2NCH(OCH_3)_2$, DMF, reflux, then cold 6 N HCl; (iii) $FeSO_4$, NH_4OH; (iv) CH_2N_2, Et_2O. (c) CH_3COCl, $SnCl_4$. (d) NH_4OAc, HOAc, PhH, reflux. (e) H_2/Pd–S. (f) *n*-PrSLi, HMPA.

(e.g., tosylate or mesylate) led to decomposition of the starting material. The failure of this reaction pathway may be attributable to the difficulty encountered in correctly aligning the reaction centers for this electrophilic substitution process.

Since this chemistry would have led, in any event, to the stereorandom production of both the cis and trans isomers of chuangxinmycin, we opted at this point to examine path A where X = O.

Pursuant to pathway A, indole **4** was acylated in quantitative yield with acetyl chloride in benzene employing stannic chloride as catalyst.[8] This product was directly subjected to an internal Knoevenagel condensation (NH_4OAc/HOAc in benzene) to afford in quantitative yield dehydrochuangxinmycin methyl ester (**6**) as a bright yellow-orange solid: mp 167–168 °C; IR ($CHCl_3$) 1710 cm^{-1}; NMR ($CDCl_3$) δ 7.92 (br m, 1 H), 6.40–6.92 (m, 4 H), 3.77 (s, 3 H), 2.30 (s, 3 H).

Since we desired to firmly establish the stereorelationship of the asymmetric centers of chuangxinmycin, we now sought an efficient procedure for reducing dehydrochuangxinmycin by hydrogenation. Because the required site of this reduction is a trisubstituted vinyl sulfide which also experiences conjugative electron release from the indolic nitrogen, we were somewhat skeptical at the outset of being able to accomplish this in an efficient manner. While numerous conditions using homogeneous and heterogeneous catalysts in various solvents with or without added traces of acid at a range of pressures were examined, only a single successful procedure has emerged to date. Hydrogenation using a sulfided 5% palladium catalyst at 70 psi in ethyl acetate provided stereochemically homogeneous chuangxinmycin methyl ester in nearly quantitative yield: mp 145–146 °C; IR ($CHCl_3$) 1730 cm^{-1}; NMR ($CDCl_3$) δ 7.88 (br m, 1 H), 6.76–7.12 (m, 4 H), 4.08 (d, 1 H, J = 4 Hz), 3.64 (overlapping m, 1 H, and s, 3 H), 1.28 (d, 3 H, J = 7 Hz); M^+ 247.0666. This ester was identical by IR, NMR, and LC with a sample prepared from natural chuangxinmycin, procured from the Peking research group, by diazomethane treatment. Since the hydrogenation can be expected to deliver hydrogen in a cis fashion to **6**, the stereorelationship of the methyl and the carboxyl substituent of **1** has been established as cis. The synthetic ester was further converted into racemic chuangxinmycin (mp 186–189 °C; M^+ 233.0511) by treatment with *n*-PrSLi in HMPA at room temperature.[9] This material was identical in all respects (TLC, IR, ^1H NMR, and MS) with the authentic sample.

In summary, this work has led to the development of an efficient synthesis of the unique alkaloid chuangxinmycin, thus rigorously establishing the relative stereochemistry of its asymmetric centers. This work further emphasizes the usefulness of the nitro group displacement reaction as a tool for the construction of diversely functionalized aromatics. Further studies in these laboratories will focus on the synthesis of selected analogues of chuangxinmycin.

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(11) Fellow of the Alfred P. Sloan Foundation.

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Chiral Recognition by ^{15}N NMR Spectroscopy. 8-Benzyl-5,6,7,8-tetrahydroquinoline[1]

Sir:

Chiral recognition through diastereomeric complex formation with optically active solvents or solutes and detected by chemical-shift differences in ^1H or ^{19}F NMR spectroscopy has many applications, including for the determination of absolute configurations.[2] The NMR shift differences observed in many chiral recognition experiments are not large and, because the reported changes of ^{15}N chemical shifts of pyridine-type nitrogens on hydrogen-bond formation and protonation are, respectively, usually 15–30 and ~100 ppm,[3] it seemed possible that differential complexation between an optically active proton donor and the separate enantiomers of chiral pyridine derivatives might lead to substantial ^{15}N chemical-shift differences. This expectation has been realized with racemic 8-benzyl-5,6,7,8-tetrahydroquinoline (**1**)[4] with several optically active acids and β-cyclodextrin[5] as complexing agents in various solvents. Most of the successful experiments

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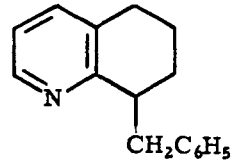
Table I. Diastereotopic Splittings in ^{15}N NMR Spectra of Racemic 8-Benzyl-5,6,7,8-tetrahydroquinoline (**1**) in the Presence of Optically Active Proton Donors at 26.5 °C

optically active compd	concn, mol %	concn of **1**, mol %	solvent	av ^{15}N shift, ppm[a]	assocn shift, ppm[b]	diastereotopic shift, Hz
R-(−)-mandelic acid	8.7	23.7	$O(C_2H_4)_2O$	70.5	(~35)	6.6
	8.0	13.5	C_2H_5OH	92.7	(~40)	5.0
	4.1	10.4	CH_2Cl_2	81.6	51.4	12.0
	6.7	16.0	CH_3CN	81.7	(~50)	0
(*S*)-(+)-lactic acid	23.0	23.0	$O(C_2H_4)_2O$	82.4[c]	23.6[c]	3.0[c]
(*R*)-(+)-$CF_3C(OCH_3)(C_6H_5)CO_2H$	2.2	10.3	CH_2Cl_2	75.6	(~67)	12.5
(*R*)-(−)-$CF_3CH(OH)C_6H_5$[d]	17.2	17.0	CH_2Cl_2	72.4	11.0	0
β-cyclodextrin hydrate	1.0	8.6	$(CH_3)_2SO$	61.4	(~10)	3.8

[a] Chemical shifts are given in parts per million upfield from external 1 M $H^{15}NO_3$ dissolved in D_2O and taken at 18.25 MHz in 25-mm tubes with a Bruker WH-180 spectrometer. [b] For a 1:1 mole ratio of **1** to complexing agent; values extrapolated to the 1:1 ratio from smaller ratios are enclosed in parentheses. [c] Measured at 15 °C. [d] Optical purity 25%.

have been done with (*R*)-(−)-mandelic acid and, as will be seen from the data in Table I, the magnitudes of the ^{15}N shift differences with the enantiomers of **1** and (*R*)-(−)-mandelic acid



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are quite sensitive to the nature of the solvent and, in general, the less polar solvents are associated with larger differential shifts. For most experiments, the proportions of proton donor to **1** were kept <1:1 with the hope of maximizing the shift differences through taking advantage of possible differences in the association equilibrium constants. In most cases, however, the degree of NMR nonequivalence of the nitrogens increased when more proton donor was added. The splittings were also found to increase with decreasing temperature. When (*R*)(+)-3,3,3-trifluoro-2-methoxy-2-phenylpropionic acid (**2**) is the complexing agent,[6] a shift difference between the nitrogens of the enantiomers in dichloromethane of 0.70 ppm was observed, and this difference, as expected, disappeared when racemic **2** was used in place of (*R*)-(+)-**2** and the average surroundings of each enantiomer of **1** become identical.

The NMR nonequivalence of the nitrogens of the enantiomers in the presence of β-cyclodextrin hydrate in dimethyl sulfoxide solution is interesting because dimethyl sulfoxide is an excellent hydrogen-bond acceptor and would be expected to saturate the hydrogen-bond-donating powers of the β-cyclodextrin. Perhaps with this combination there is some tendency for preferential insertion of the phenyl ring of one of the enantiomers of **1** into the chiral void of the β-cyclodextrin.

The origin(s) of the shift differences produced by complexing optically active acids with **1** is uncertain. The ^1H NMR of the $>CHCH_2C_6H_5$ moiety of **1** indicates a strong preference for one rotational conformation at the C-8–C-9 bond which, from inspection of models, almost certainly has the benzyl group opposite to the pyridine ring.[7] With a carboxylic acid having a chiral center at the α carbon, the diastereomeric centers would be rather far apart in a hydrogen-bonded complex. Nonetheless, if the benzyl group is in essentially a single conformation, there will be a substantial molecular dissymmetry extending away from the chiral center. The total change of 23.6–67 ppm in ^{15}N NMR shift when **1** is complexed with carboxylic acids (see Table I) is pretty much in the range expected for hydrogen bonding to pyridine,[3,8] and probably represents only a small degree of actual proton transfer and ion-pair formation.

Further experiments are underway to determine the scope of this kind of chiral recognition and its possible applicability to the determination of absolute configurations of pyridine bases or proton donors.

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Electron Nuclear Double Resonance of Ferric Cytochrome $P450_{CAM}$

Sir:

We have used electron nuclear double resonance (ENDOR) to probe the heme environs of cytochrome $P450_{CAM}$, isolated from the prokaryote *Pseudomonas putida*. We studied the native, substrate-free, low-spin ferric m^o and the high-spin ferric component of the enzyme-substrate complex, m^{os}. The ENDOR of the low-spin m^o form showed at least one strongly coupled, exchangeable proton attached to an axial ligand of the heme iron, in good agreement with the interpretation of previous proton relaxation studies.[1] The high-spin m^{os} showed no evidence for histidine or water ligation and indicated five coordination of the heme iron.

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