C-22, and C-23 to be 106.6 (4), 105.1 (4), 104.9 (4), and 107.4 (4)°, respectively, which are substantially smaller than found (121 and 124°) for the corresponding angles of Ni(HDMG)$_2$.[14]

The small magnitude of these angles presumably increases the C-C-N angles in the chelate ring to the point where formation of a larger ring by N-O coordination becomes more favorable. However, even in the six-membered ring there appears to be some strain due to the sharp angle (94.2 (2) and 93.9 (2)°) at the Ni in the chelate ring. Thus all the following angles in the ring are larger than corresponding angles in Ni(HDMG)$_2$ (the given angle is listed first followed by the corresponding angle in the other ring): N-3-C-23-C-22, 122.1 (5), 122.9 (5)°; N-4-C-22-C-23, 132.0 (5), 129.6 (4)°; Ni-N-3-C-23, 124.8 (4), 126.3 (3)°. These unusually large angles suggest that the six-membered chelate rings may also be strained. The delicate balance between N-O and N-N coordination in HCQD$^-$ complexes is supported by the fact that we find the ligand to be N-N coordinated in Cu(HCQD)$_2$. The now known existence of these two modes of bonding suggests that N-O-bonded forms may be present as intermediates in reactions of complexes of other α-dioxime ligands.

Although the O-1-O-4 and O-2-O-3 distances (2.49 and 2.50 Å) are not so short as those (2.40 Å)[14] in Ni(HDMG)$_2$, it appears that some hydrogen bonding does occur. There are no short distances which permit intermolecular hydrogen bonding. The molecules pack in the unit cell such that the closest distance between Ni atoms in parallel complexes is one unit cell length (12.031 Å) along the *c* axis. Thus there is no Ni-Ni interaction such as occurs in Ni(HDMG)$_2$.[14]

The infrared spectrum of Ni(HCQD)$_2$ taken in a KBr pellet shows a medium-intensity absorption at 1690 cm^{-1}, an unusually high frequency uncharacteristic of N-bonded α-dioxime ligands.[15] Deuteration studies indicate that the band is not associated with the OH group but presumably arises from a vibration which has considerable C=N stretching character. This absorption may allow easy identification of other complexes which contain α-dioxime ligands coordinated via their N and O atoms.

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Supplementary Material Available. Fractional coordinates and thermal parameters (Table I), bond distances (Table II), important bond angles (Table III), and structure factors (14 pages). Ordering information is given on any current masthead page.

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Preparation of Macrolides via the Wittig Reaction. A Total Synthesis of (−)-Vermiculine

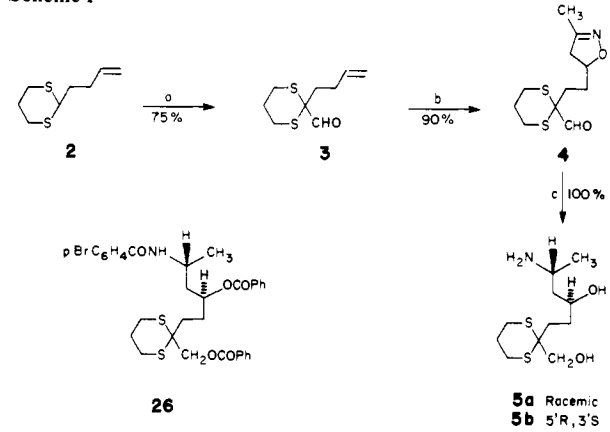
Sir:

The antibiotic (−)-vermiculine (**1**) was isolated in 1972 from the fermentation broth of *penicillium vermiculatum* Dangeard.[1] The originally proposed structure of a nine-membered lactone[2] was revised to that of the 16-membered dilide system **1** on the basis of an X-ray analysis.[3] Subsequently, two nonstereospecific syntheses of (±)-vermiculine were published.[4] More recently, a stereospecific synthesis via an optically active synthon of known chirality produced the unnatural enantiomer of vermiculine, allowing the 8*S*,16*S* configuration to be assigned to the natural product.[5] A feature common to all of the above syntheses is the formation of the macrolide ring by lactonization.

We would like to record the total synthesis of natural (−)-vermiculine (**1**). In our scheme (Scheme I), the Wadsworth-Emmons modification of the Wittig reaction serves to achieve the critical closure of the macrolide ring. Although this principle has been used for the construction of smaller rings,[6] we are aware of only one application to macrolide synthesis.[7]

The dithiane olefin **2**[8] was transformed into the aldehyde **3** (bp 100–104 °C (0.5 mm)) via its lithium salt in standard fashion[9] (Scheme I). In a 1,3-dipolar cycloaddition, acetonitrile oxide was added regiospecifically[10] to the terminal double bond to yield the isoxazoline **4** (mp 72–73 °C). Simultaneous aldehyde reduction and cleavage of the isoxazoline ring occurred upon treatment with diisobutylaluminum hydride, producing stereospecifically the aminodiol **5a.** Its relative configuration is the result of hydride addition to the imino double bond from the less hindered side of the isoxazoline ring in **4,** apparently prior to the cleavage of the N-O bond.[11]

Scheme I[a]



[a] (a) BuLi, then DMF, THF, −30 °C → room temperature. (b) PhNCO, $EtNO_2$, NEt_3 catalyst, PhH. (c) *i*-Bu_2AlH, THF, 55 °C.

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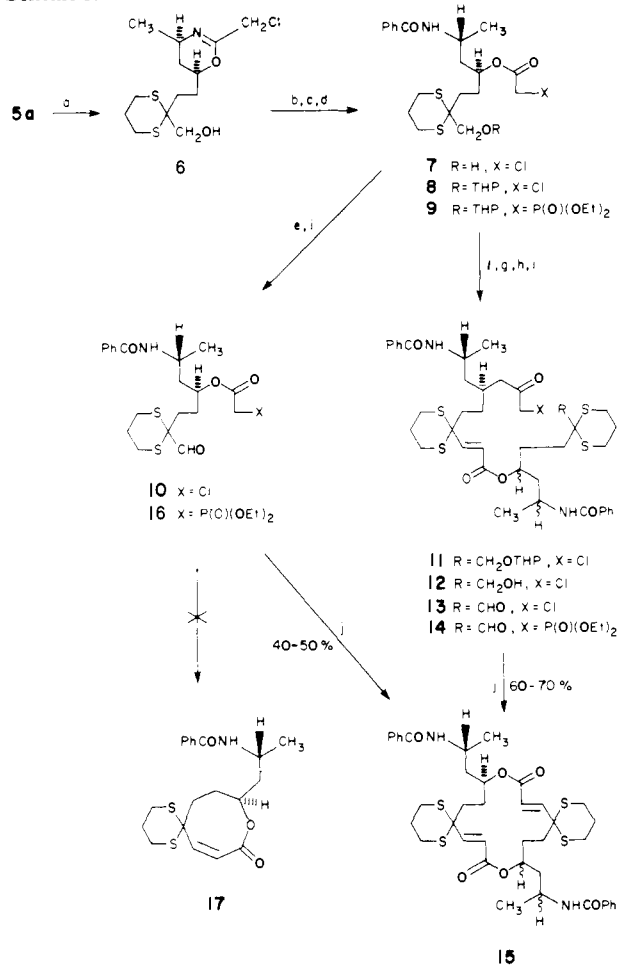
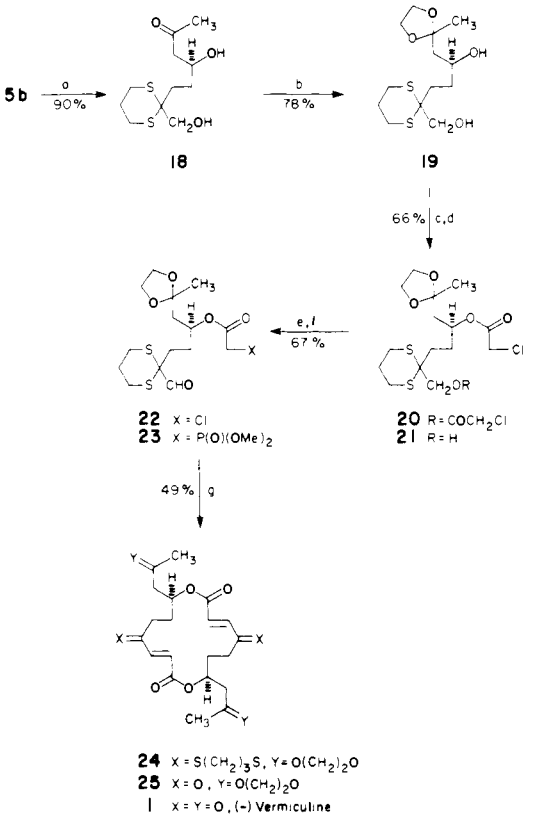
Scheme II[a]



[a] (a) $ClCH_2C(=NH)OEt \cdot HCl$, NEt_3, CH_2Cl_2, 45 °C. (b) CF_3CO_2H-H_2O, evaporation, then PhCOCl, NEt_3, $CHCl_3$. (c) Dihydropyran, *p*-TsOH, CH_2Cl_2. (d) $P(OEt)_3$ neat, 95 °C. (e) Me_2SO, $(CF_3CO)_2O$, NEt_3, CH_2Cl_2, −40 °C → room temperature. (f) NaH, THF, then **10**. (g) HCl, CH_2Cl_2–Et_2O. (h) As in e. (i) As in d. (j) NaOEt or NaH, THF.

Scheme III[a]



[a] (a) 3,5-Di-*tert*-butyl-*o*-benzoquinone, MeOH. (b) 2-Methyl-2-ethyl-1,3-dioxolane, $BF_3 \cdot Et_2O$. (c) $(ClCH_2CO)_2O$, NEt_3, $CHCl_3$. (d) Na_2CO_3 catalyst, EtOH–H_2O (5:1). (e) Me_2SO, $(CF_3CO)_2O$, NEt_3, CH_2Cl_2, −40 °C → room temperature. (f) $P(OMe)_3$, neat, 90 °C. (g) NaH, THF.

The potential of the Wittig reaction for the closure of a macrolide ring was now tested in a model study. Thus, condensation of **5a** with ethyl 2-chloroethanimidate[12] gave the labile 5,6-dihydro-4*H*-1,3-oxazine **6** (Scheme II). Subsequent ring opening[13] and protective in situ N-acylation resulted in formation of the more stable chloroacetate intermediate **7.** The following transformations served to achieve a stepwise coupling of units derived from **7.** First, the protected tetrahydropyranyl ether **8** was converted to the phosphonate **9.** Second, the aldehyde component **10** (mp 118–120 °C), also prepared from **7** by the oxidation method of Omura, Sharma, and Swern,[14] was then condensed with the anion of **9** to furnish the protected trans olefin **11.** The regenerated primary carbinol **12** was oxidized[14] to the aldehyde **13,** and the chloride was then displaced to give the phosphonate aldehyde **14.**

Having thus established the appropriate functional groups, the stage was set to effect ring closure by the Wittig reaction. Indeed, when **14** was subjected to 1 equiv of a base at high dilution,[15] cyclization took place at ambient temperature, yielding predominantly the desired dilide system **15** as a 1:1 mixture of *dl* (mp 248–250 °C) and meso (mp 246–248 °C) diastereomers. When the more accessible monomeric precursor **16** was exposed to these same conditions,[15] *the product mixture consisted similarly of an equal amount of dl and meso* **15** (~45% yield), along with some larger cyclic "oligomers". No pure intramolecular ring closure to the hypothetical eight-membered lactone **17** occurred. As a consequence of this failure of **16** to react intramolecularly, the dilide **15** becomes the most favored product at high dilution.

From these studies we concluded that the synthetic target vermiculine, owing to its C_2 symmetry, could be approached straightforwardly by combining two chirally identical synthons related to **16.** To this end, the racemic aminodiol **5a** was resolved by means of the camphorsulfonic-*d* acid (CSA) salt.[16] The free base **5b** (mp 79–81 °C, $[\alpha]_D$ +2.80° (*c* 2, 1 N HCl)) of the desired 5′*R*,3′*S* configuration was recovered quantitatively from the CSA salt with sodium hydroxide treatment, and its absolute structure was determined by an X-ray of the derivative **26** (mp 167–169 °C, $[\alpha]_D$ +5.90° (*c* 1, MeOH)) (Scheme I).

The aminoalkyl residue of **5b** was modified by oxidation[17] to the ketone **18** (Scheme III) and protection as the dioxolane **19.** Differentiation of the two alcohol functions of **19** was achieved conveniently by exhaustive acylation to the bis ester **20,** followed by liberation of the desired primary carbinol **21** by a selective transesterification.

Oxidation[14] to the aldehyde **22** (mp 61–64 °C, $[\alpha]_D$ +2.91° (*c* 1, $CHCl_3$)) and treatment with trimethyl phosphite gave the phosphonate aldehyde **23** in 31% overall yield from **5b.** Direct application of the reaction conditions[15] established for the previous "dimerizing cyclization" gave the dilide **24** (mp 163–166 °C, $[\alpha]_D$ −58.11° (*c* 0.6, $CHCl_3$)), free of the undesired meso isomer.

The scheme for the conversion of the macrolide **24** to (−)-vermiculine (**1**) is similar to that employed in the synthesis of (±)-pyrenophorin.[18] In the case of **24,** the procedures examined for the removal of the dithiane protecting groups were unsatisfactory. We discovered, however, that brief treatment

with *N*-iodosuccinimide[19] cleaved the bisdithiane **24** smoothly to the diketone **25** (mp 117.5–118.5 °C, $[\alpha]_D$ +13.88° (*c* 0.5, $CHCl_3$)) in 90% yield. The 2-oxopropyl side chains were then restored by trans ketalization with boron trifluoride etherate in acetone, furnishing, after recrystallization from acetic acid, pure (−)-vermiculine (**1**) (mp 177–178 °C, $[\alpha]_D$ −10.6° (*c* 0.2, $CHCl_3$)) as colorless prisms in 90% yield, identical in all respects with the natural product.[20]

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(16) The CSA salt of **5b** (mp 178–179 °C, $[\alpha]_D$ +24.16° (*c* 2, MeOH)), obtained in 66% recovery by addition of 0.5 equiv of CSA to a CH_3CN solution of **5a** followed by one recrystallization from CH_3CN–MeOH, was of sufficient optical purity for the ensuing transformations.
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(19) The best conditions were found to be 12 equiv of NIS (6 min, −7 °C) in acetone–H_2O (19:1), followed by quenching with aqueous $Na_2S_2O_3$ solution.
(20) We thank Professor J. D. White for providing us with an authentic sample of natural vermiculine for comparison of the CD and ORD spectra.
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Poly(cinchona alkaloid-*co*-acrylonitrile)s. New Polymer Catalysts for Asymmetric Synthesis[1]

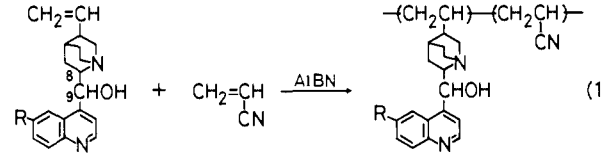
Sir:

The catalytic activities of cinchona alkaloids in asymmetric organic reactions have been extensively studied.[2] The principal drawback in the use of the alkaloid catalyst is the relative difficulty of separating the product from the catalyst. One way to overcome this drawback would be to fix the alkaloid on a solid support in a way that retains the stereoselectivity of the alkaloid (eq 1).

Table I. Copolymerization of Quinine with Acrylonitrile[a]

entry	quinine/ acrylonitrile	polymer yield, %	η_{inh}[b]	$[\alpha]_D$, deg[c]	quinine content, mol %[d]
1	1:20	51.4	0.23	−15.7	3.2
2	1:15	42.0	0.20	−19.4	4.2
3	1:9	28.8	0.20	−24.8	5.8
4	1:4	17.9	0.16[e]	−37.0	9.9
5	1:3	11.4	0.13	−41.8	12.0

[a] Reaction conditions: acrylonitrile, 1.59 g (30 mmol); AIBN, 0.04 g (0.24 mmol); chloroform, 10 mL; refluxing for 44 h with stirring under argon. [b] Measured in DMF at 30 °C. [c] Measured in DMF at 28 °C. [d] Calculated from the analytical data. [e] $\overline{Mn}$ 3800.



(1)

Quinine, Quinidine; R = OCH_3
Cinchonine, Cinchonidine; R=H

In designing such a polymeric alkaloid, it has to be taken into account that the amino alcohol part of the alkaloid, N(1)–C(8)–C(9)–OH, generally plays an crucial role in asymmetric reactions: the configurations at C(8) and C(9) in the alkaloid are of fundamental importance in determining the configuration of products; in addition, modification of the hydroxyl or amino group affects significantly the extent of stereoselectivity, usually in the direction of lowering optical yields.[3,4] In this respect the previously known polymeric cinchona alkaloids, in which the alkaloid moiety is anchored in either O-acylated form[5] or N-alkylated form,[6] seem to have limited potential as catalysts for asymmetric synthesis.

Accordingly, we investigated the utilization of the vinyl group of the alkaloids as the connecting site to polymers.[7] We report herein a remarkably general procedure for the synthesis of new polymeric cinchona alkaloids, in which the amino alcohol part can be free or protected, and demonstrate their potential as asymmetric catalysts. Our procedure is based on the radical copolymerization of cinchona alkaloids with vinyl monomers. This is the first report of vinyl polymerization of cinchona alkaloids.[8]

Of the various vinyl monomers examined, acrylonitrile showed the highest copolymerizability with the alkaloids.[9] Copolymerization of cinchona alkaloid with acrylonitrile was carried out using azobisisobutyronitrile (AIBN) as an initiator under an inert gas atmosphere. A typical experimental procedure follows. A solution of quinine (7.5 mmol), acrylonitrile (30 mmol), and AIBN (0.24 mmol) in chloroform (10 mL) was stirred magnetically for 44 h with refluxing. The precipitated polymer was filtered, washed with methanol, reprecipitated from DMF into methanol, and dried at 70 °C under a vacuum. Table I summarizes the representative results of quinine–acrylonitrile copolymerization.

All the polymers had negative rotations. The IR spectra (KBr) showed bands at 1620, 1590, 1245, and 1230 cm^{-1} characteristic of quinine, and a band at 2250 cm^{-1} due to nitrile groups. The polymer gave ^1H NMR spectra (Me_2SO-d_6, 100 MHz, δ) without signals due to allylic protons: in the 4.8–6.1 region only two signals due to H–O (~5.2) and H–C(9) (~5.6) were observed. Since quinine is resistant to homopolymerization under the conditions employed, it was

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