Application of cyclization mode **1** → **2** involving the use of appropriate terminating groups to selected naturally occurring steroid cases, such as 3β,5β-dihydroxycardenolides as well as 11-oxygenated and Δ^4-3-ketone types, is apparent and planned.

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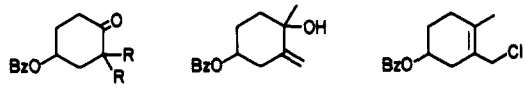
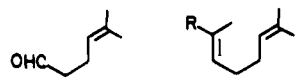
(6) Synthesis: 4-Benzyloxycyclohexanone (i) was transformed into the corresponding α-methylene ketone (ii) by a modification of the method of G.



i R=H *iii* *iv*
ii R,R=CH_2

M. Ksander, J. E. McMurry, and M. Johnson, *J. Org. Chem.*, **42**, 1180 (1977). Treatment with diethyl oxalate and $NaOC_2H_5$ (EtOH, 0 °C to room temp.), gave 63% ethyl-2-oxalyl-4-(phenylmethoxy)cyclohexanone, which without purification provided ii after successive reactions (THF, 0 °C) with NaH and gaseous formaldehyde. After conversion (41%) of unisolated ii into tertiary alcohol iii by methyllithium in ether at −78 °C, addition of thionyl chloride to the Li salt of iii (THF, −78 °C) generated allylic halide iv, directly convertible (58% from iii) by lithium thiophenoxide (THF, 0 °C to room temperature) into thioether (±)-**3**: NMR (100 MHz, $CDCl_3$) δ 1.46 (br s, 3 H) ($C{=}CCH_3$), 3.43 (d, J = 11.9 Hz, 1 H) and 3.61 (d, J = 12.3 Hz, 1 H) (CH_2S–), 3.60 (m, 1 H) (CHO–), 4.58 (s, 2 H) (OCH_2–), 7.10–7.49 (m, 10 H) (ArH); IR (neat) 1590, 1030, 741, 694 cm^{-1}.

(7) Synthesis: The heptenaldehyde v was transformed by $(EtO)_2POCH(CH_3)$-CO_2Et [NaH, $(CH_3O)_2(CH_2)_2$, 10–30 °C, 46%] into the trans ester vi, bp 91–95 °C (2 Torr). AlH_3 reduction (Et_2O, −10 to 5 °C, 93%) provided alcohol vii, which, after conversion (*n*-BuLi–*p*-tosyl chloride, THF, 0 °C to



v *vi* R=CO_2Et
vii R=CH_2OH

room temperature) to unisolated *p*-tosylate and treatment with lithium thiophenoxide (0 °C to room temperature) gave (56%) thioether **5**: NMR (100 MHz, $CDCl_3$) δ 1.57 (s, 3 H), 1.66 (s, 3 H), and 1.73 (d, J = 0.6 Hz, 3 H) ($C{=}CCH_3$), 1.94 (m, 4 H) ($C{=}CCH_2$), 3.49 (s, 2 H) (SCH_2), 5.03 (m, 1 H) and 5.24 (m, 1 H) ($C{=}CH$), 7.11–7.44 (m, 5 H) (ArH); IR (neat) 1660, 1580, 736, 688 cm^{-1}.

(8) For an alternative, previous preparation of sulfide **5**, see K. A. Parker and W. S. Johnson, *J. Am. Chem. Soc.*, **96**, 2556 (1974).
(9) J. F. Biellmann and J. B. Ducep, *Tetrahedron*, **27**, 5861 (1971).
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(11) This substance was accompanied by a congener with a signal at δ 2.66–2.67.
(12) K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.*, **95**, 6136 (1973).
(13) The synthesis of sterol derivatives **8** and **9** will be described elsewhere.
(14) Prepared by $NaBT_4$ reduction of the α,β-unsaturated ketone resulting from successive treatment of (±)-**10** with NH_3–methanol, CrO_3–aqueous H_2SO_4–acetone, *p*-TsOH–benzene.
(15) Obtained from the known[16] 20-methylpregna-4,20-dien-3-one by $SnCl_4$-induced ring-D rearrangement followed by $Li(t\text{-}C_4H_9O)_3H$ reduction.
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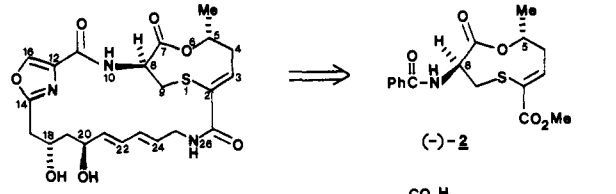
Studies Directed toward the Total Synthesis of Streptogramin Antibiotics. Enantiospecific Approach to the Nine-Membered Macrocycle of Griseoviridin

Sir:

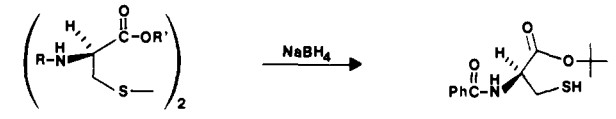
The streptogramin family of antibiotics are broad spectrum acting and are comprised of at least two active compounds, one being mainly peptidic in nature, the other consisting of a 23-membered ring (e.g., griseoviridin, **1**).[1] This class of antibiotics was first discovered in the culture of *Streptomyces graminofaciens*[2] in 1953 and extensive structure elucidation studies have been performed since that time.[3] Recently, the structure of griseoviridin (**1**) was confirmed by X-ray techniques.[4] The most obvious retrosynthetic analysis of **1** requires that it be formed by a convergence scheme comprised of the two fragments, **2** and **3**,[5] and it is the purpose of this report to outline



1 (-)-**2** **3**

our successful stereospecific synthesis of the nine-membered macrocycle **2** in pure enantiomeric form. Inspection of the target antibiotic reveals, in addition to a wide array of functionality, the presence of a rare D-amino acid (C-8) and other chiral centers at C-5, C-18, and C-20. Two of these chiral centers, as well as the lactone and thiovinyl ether linkages, are present in the nine-membered macrocycle **2** which possesses the 5*R*,8*S* configuration.

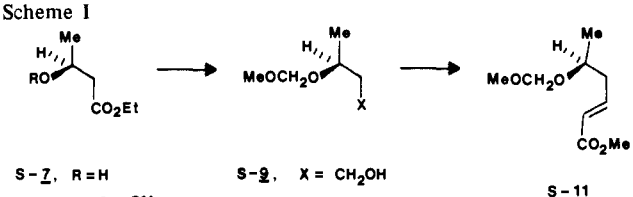
The stereospecific approach to **2** originates from D-cystine[6] (**4**) which was transformed into the bis *tert*-butyl ester (60% $HClO_4$, *tert*-butyl acetate, 25 °C, 2 days) and treated immediately thereafter with benzoyl chloride in pyridine (0–25 °C, 15 h) to afford the *N*-benzoyl derivative **5** [mp 159–160 °C, $[\alpha]_D$ + 24.4° ($CHCl_3$), 85%].[7] Reduction with sodium borohydride in ethanol gave the (*S*)-cysteine **6** in 82% yield [mp



S-(+)-**4**, R = R' = H
5, R = PhCO, R' = *t*-Bu
S-(-)-**6**

95–99 °C, $[\alpha]_D$ −39.6° ($CHCl_3$)].[7] The C-2–C-5 fragment in the nine-membered ring of **2** was stereospecifically constructed as outlined in Scheme I. Ethyl acetoacetate was treated with bakers yeast (28–30 °C, 3 days) to afford the

Scheme I



S-**7**, R=H
S-**8**, R=CH_2OMe
S-**9**, X = CH_2OH
S-**10**, X = CHO
S-**11**

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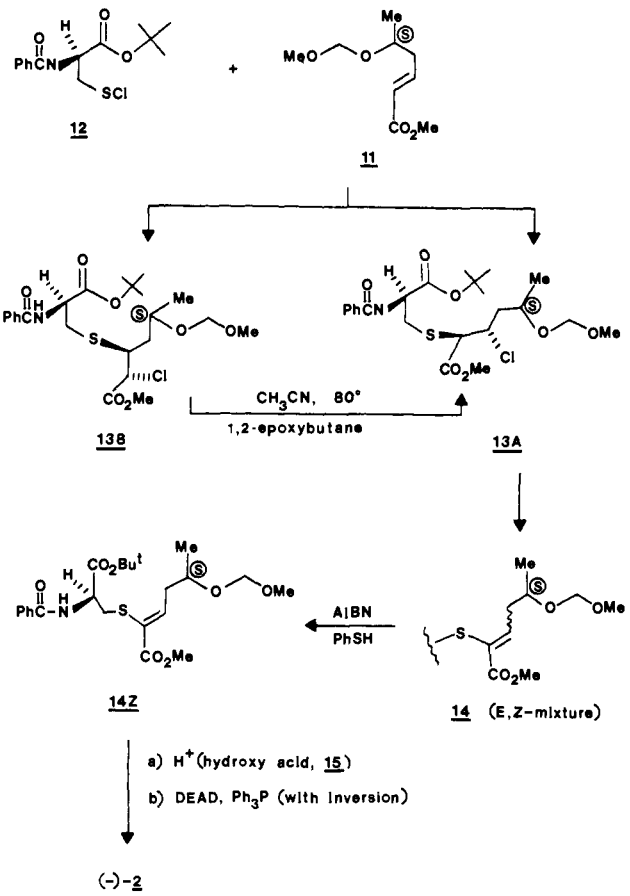
Scheme II

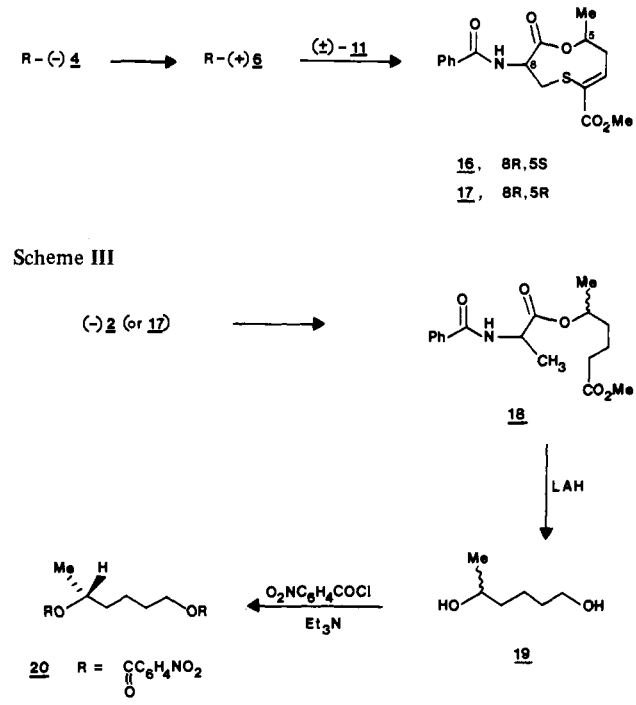


chiral alcohol **7** in 64% yield[8] [$[\alpha]_D$ + 41.7° ($CHCl_3$)] which proved to be >97% ee via ^1H NMR shift studies.[9] The hydroxyl group was protected as the acetal **8** ($ClCH_2OMe$, *N,N*-diethylaniline, 25 °C, 3 days, 89% yield) and then reduced to the alcohol **9** [$LiAlH_4$, Et_2O; $[\alpha]_D$ +83.8° ($CHCl_3$), 85% yield].[7] Oxidation (oxalyl chloride-Me_2SO, −60 °C) using the Swern technique[10] gave aldehyde **10** in quantitative yield,[7] which was homologated to the pure *E* α,β-unsaturated ester **11** by the Wadsworth-Horner-Emmons reaction [85%, $[\alpha]_D$ + 1.04° (neat), −0.38° ($CHCl_3$)].[7]

The next task to be performed involved the joining of the protected (*S*)-cysteine **6** and the protected α,β-unsaturated ester (*S*)-**11.** This was accomplished via the sulfenyl chloride **12** prepared in situ from **6** (*N*-chlorosuccinimide, CH_2Cl_2, 25 °C) and treated immediately with **11** to give a 56% yield of **13A** and **13B** (Scheme II) in the ratio of 1:4.[11] The mixture was transformed into a single regioisomer **13A** by heating in acetonitrile containing epoxybutane as a proton scavenger. The crude α-thio-β-chloro ester **13A** was next subjected to elimination (Et_3N-CH_2Cl_2, 25 °C, 1 h) and furnished **14** as an *E*:*Z* mixture (70% *Z*, 30% *E*). The mixture was smoothly homogenized into a single *Z* isomer **14** by reversible addition of a phenyl thiyl radical[12] (10 mol % PhSH; 2 mol % AIBN). The yield of **14***Z* was 86-95%.[13]

To prepare for the ring closure to (−)-**2**, the methoxymethyl and *tert*-butyl groups were removed simultaneously (10% HCl-DME, 65 °C, 6 h) furnishing the hydroxy acid **15** (75%, mp 129-132 °C, $[\alpha]_D$ +2.67°).[7] The ring closure was performed with reagents known to give inversion[14] at the carbinol center since it was necessary to arrive at the 5*R* configuration in the final product. Toward this end, the hydroxy acid **15** was treated with triphenylphosphine-diethyl azodicarboxylate[15] (benzene, 25 °C, 65 h) and gave the macrocyclic lactone **2** in 47% yield[16] (mp 125.5-126.5 °C). The entire scheme was also performed using the (*R*)-cystine **4** and racemic **11.** In this instance two diastereomer **16** and **17** were isolated (preparative TLC) in almost equal amounts and characterized. Except for specific rotations, the IR, NMR, and mass spectra were virtually identical with those of (−)-**2**. It was shown that **16** [mp 124.5-126 °C, $[\alpha]_D$ +122.2° (*c* 1, $CHCl_3$)] was the enantiomer of (−)-**2** [i.e., (+)-**2**] where the other diastereomer **17** was epimeric at C-5. To confirm that inversion at C-5 had indeed occurred in the scheme **14Z** → **15** → **2** using the DEAD-Ph_3P reagent, (−)-**2** (or **17**), both presumably with 5*R* configurations, were subjected to Raney nickel desulfurization to the ester **18** (ethanol, 80 °C) which was further reduced ($LiAlH_4$, THF) to the diol **19** (Scheme III). The crude diol was transformed into the known dibenzoate[17] [mp 105-106 °C, $[\alpha]_D$ −33° (*c* 0.26 $CHCl_3$)] with good agreement. Thus, the configuration at C-5 and the inversion of the (*S*)-carbinol in **15** appear to be on firm ground. The synthesis of (−)-**2** was therefore accomplished in a stereospecific manner requiring no separations of enantiomers. The synthetic approach to **1** and its related macrocycles will be described in future reports.

Scheme III



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(9) Examination of racemic **7** and that derived by yeast reduction using [tris(3-heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) indicated the total absence of enantiomeric carbinol.
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(13) Physical data for **14Z**: $[\alpha]_D$ −62.97° ($CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.70-7.95 (m, 2 H), 7.05-7.60 (m, 5 H), 4.65-5.00 (m, 1 H), 4.60 (s, 2 H), 3.60-4.05

(m, 1 H), 3.64 (s, 3 H), 3.20–3.45 (m, 2 H), 3.30 (s, 3 H), 2.67 (br t, J = 6 Hz, 2 H), 1.50 (s, 9 H), 1.18 (d, J = 6 Hz, 3 H).
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(16) Physical data for (−)-**2**: $[\alpha]_D$ −123.4° (c 1, $CHCl_3$); IR (KBr) 3310, 1741, 1713, 1638 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25–7.95 (m, 6 H), 7.08 (br d, J = 6 Hz, 1 H), 4.80–5.50 (m, 2 H), 3.80 (s, 3 H), 3.15–3.60 (m, 2 H), 2.20–3.15 (m, 2 H), 1.34 (d, J = 6 Hz, 3 H); mass spectrum m/e 349 (M^+) with no higher peaks present.
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Inelastic Electron Tunneling Spectroscopy of Zirconium Tetraborohydride Supported on Aluminum Oxide

Sir:

Currently, there is significant interest in newly developed supported-complex catalysts, which are formed by anchoring or grafting a homogeneous catalyst (a cluster compound) onto a high surface area support.[1] Such catalysts can combine the activity and selectivity found in homogeneous systems with the stability and ease of separation characteristic of heterogeneous catalysts, and they frequently exhibit activities an order of magnitude or more greater than the corresponding unsupported systems.[2] Progress in this area, however, has been hampered by a lack of detailed structural information for supported complexes. Characterization of supported complexes has been poor, plagued by many of the same problems that arise in attempting to characterize traditional heterogeneous catalysts; and, as yet, there are not reported cases where the structure of a supported complex has been definitely determined, at least employing vibrational spectroscopy. We report here the vibrational spectrum of the supported complex formed by the interaction of zirconium tetraborohydride, $Zr(BH_4)_4$, a known homogeneous polymerization catalyst for olefins, with an alumina surface. This vibrational information was obtained utilizing inelastic electron tunneling spectroscopy (IETS).

IETS involves monitoring the current due to electrons tunneling inelastically through a thin insulating barrier between two metal electrodes. Although most of this tunneling current is elastic, some electrons can tunnel inelastically by exciting vibrational modes of molecules at, or near, the surface of the insulating barrier. Such inelastic transitions can occur only when the bias voltage across the barrier is greater than, or equal to, a vibrational excitation energy, and lead to increases in conductance across the barrier by providing additional channels for electron tunneling. These conductance increases become peaks when the second derivative of voltage with respect to current, d^2V/dI^2 (proportional to d^2I/dV^2), is plotted as a function of the bias voltage, V. Peak positions correspond to vibrational excitation energies and yield information analogous to that obtained by optical absorption spectroscopies. Both IR and Raman active modes are observed in the IET spectra. Further theoretical and experimental details are available elsewhere.[3]

In our experiments, the top few atomic layers of a freshly evaporated Al film were oxidized to form the thin insulating barrier. The $Zr(BH_4)_4$ was then allowed to adsorb on the resultant aluminum oxide surface. Saturation coverage was obtained by exposure to 5×10^{-2} Torr of $Zr(BH_4)_4$ for 15 min. The samples were completed by evaporation of top metal (Pb) electrode. Measurements were made over the entire spectral range from 240 to 4000 cm^{-1}, with a resolution on the order of 4 cm^{-1} and a sample surface area of ~1 mm^2. An IET spectrum for a saturation coverage of $Zr(BH_4)_4$ on aluminum oxide at 300 K is shown in Figure 1. Peak positions are also indicated in the figure.

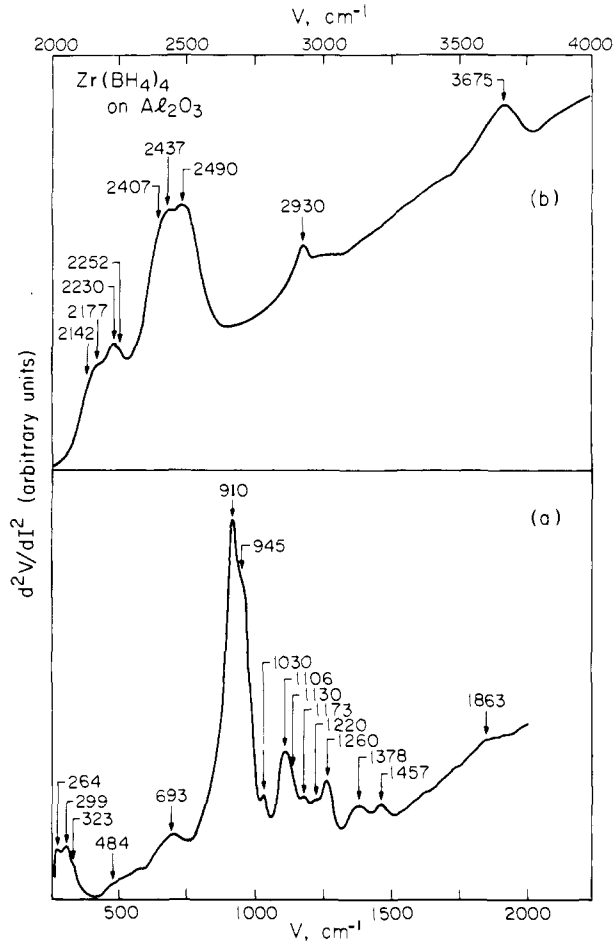

Figure 1. IET spectrum for $Zr(BH_4)_4$ supported on Al_2O_3 at 300 K over the energy range (a) 240–2000 cm^{-1} and (b) 2000–4000 cm^{-1}.

Comparisons with IETS studies of "clean" Al_2O_3 indicate that the spectral features at 299, 945, and 1863 cm^{-1} can be assigned to a phonon in the underlying Al film, a bulk Al–O stretching mode, and its harmonic overtone, respectively.[4] The 3675-cm^{-1} peak is the O–H stretching vibration of surface hydroxyl groups, while the peak near 2930 cm^{-1} arises from the C–H stretching vibration of a small amount of adsorbed hydrocarbon contamination.[4] Contamination might also contribute to the intensity of features at 1030 cm^{-1} and in the 1300–1500-cm^{-1} region.

The boron atoms in $Zr(BH_4)_4$ are arranged tetrahedrally, each being bound to the central Zr atom in a tridentate manner with three bridging hydrogens.[5] During adsorption, one or more of the BH_4 ligands are lost as the Zr becomes either singly or multiply coordinated to oxygen atoms on the surface.[2] Since the surface becomes a virtual ligand, it might well affect bonding in the remaining BH_4 groups. For example, $(C_5H_5)_2Zr(BH_4)_2$ and $(C_5H_5)_2Zr(H)BH_4$ are both known to have bidentate bridging structures,[6] and the surface could be expected to have a similar effect. Information concerning bonding can be obtained by examining the stretching vibrations of both terminal (H_t) and bridging (H_b) hydrogens. The B–H_t region shows at least three peaks near 2407, 2437, and 2490 cm^{-1}. For the tridentate structure, only one (possibly broadened) peak at 2560–2580 cm^{-1} is to be expected.[7] The observed frequencies are more closely related to those reported

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