interaction has been considered a limiting model for the C–H–M interaction,[22] and this point is clearly illustrated by these two isoelectronic compounds. Futhermore, if the Fe–H–C interaction observed in $HFe_4(CH)(CO)_{12}$ is taken to represent the initial stage of the cleavage of a C–H bond on a metal surface, the Fe–H–B interaction in I models the cleavage further along the reaction coordinate. Thus, not only are metalloboranes useful synthetic intermediates,[23] but compounds such as I and $B_2H_6Fe_2(CO)_6$ can be used as reasonable models for hydrocarbons in metal-bonding configurations that may be intrinsically unstable and, hence, unable to be isolated. Further details of this and related studies will be published in due course.

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Registry No. I, 80572-82-3.

Supplementary Material Available: List of atomic coordinates and thermal parameters for $HFe_4(BH_2)(CO)_{12}$ (4 pages). Ordering information is given on any current masthead page.

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Total Syntheses of (±)-Pseudomonic Acids A and C

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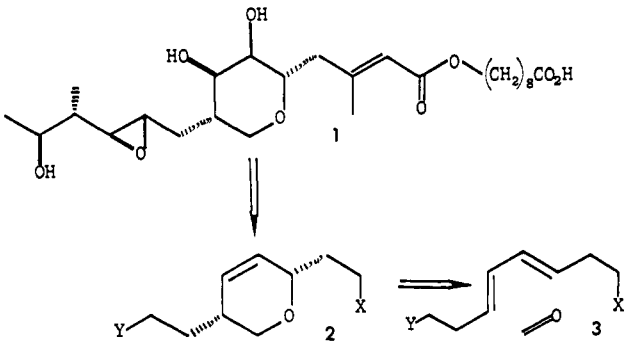
Pseudomonic acid A (**1**), an antibiotic produced by a strain of *Pseudomonas fluorescens*, functions as a competitive inhibitor of isoleucyl-tRNA synthetase[2] and is an effective antimicrobial agent against gram-positive bacteria, *Haemophilus influenzae*, *Neisseria gonorrhoeae*, and mycoplasmal pathogens.[3] The absolute and relative stereochemistry have been determined by spectroscopic studies[4] and X-ray analysis.[5] More recently, pseudomonic acid C, with a double bond instead of an epoxy group in the side chain, has been isolated.[6] The novel structure and complex stereochemistry and functionality of pseudomonic acid have made it a popular synthetic target.[7,8]

Our approach was based on the retrosynthetic analysis shown in Scheme I. The vicinal diol of pseudomonic acid can easily be constructed from the double bond of **2** and the two side chains can be elaborated from differently functionalized two-carbon fragments. The dihydropyran **2** can be made by a Diels–Alder reaction of **3** and formaldehyde. Since we have recently shown that Me_2AlCl is an efficient catalyst for the Diels–Alder reaction of aldehydes and dienes,[9] this is an attractive approach if the

Scheme I



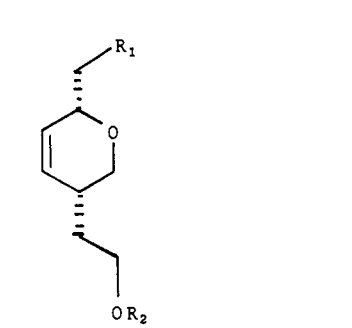
regiochemistry of the Diels–Alder reaction can be controlled.

We have developed a novel and potentially general approach to control this regiochemistry which we term a quasi-intramolecular Lewis acid catalyzed Diels–Alder reaction. Complexation of both the diene and dienophile to the Lewis acid (e.g., **9**) leads to the regiochemical, and possibly sterochemical, control typical of intramolecular Diels–Alder reactions. The success of this approach depends on the reaction of an alkylaluminum halide with a functional group in the diene, such as an alcohol, to give a complex which loses an alkane to generate a new Lewis acid containing the diene moiety which can complex to the dienophile.

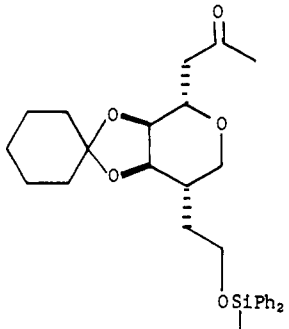
This method can be applied to the synthesis of pseudomonic acid by treating **3**, X = OH, with $RAlCl_2$. The resulting complex will irreversibly lose an alkane (RH) generating an alkoxyaluminum dihalide which can complex to formaldehyde. The resulting complex will undergo a quasi-intramolecular Lewis acid catalyzed Diels–Alder reaction. In turn, the required homoallylic alcohol **3**, X = OH, should be available by an alkylaluminum halide catalyzed ene reaction of formaldehyde with the terminal double bond of **6**.[9]

The desired acetate **6** is easily constructed from 1,5-hexadiene (**4**) by a Me_2AlCl catalyzed ene reaction with formaldehyde (0.9 equiv of CH_2O, 1.4 equiv of Me_2AlCl, 30 min, 0 °C) which gives **5** as an 8:1 mixture of trans and cis isomers in 80% yield. This mixture is used without purification since ene adducts derived from the cis isomer of **6** will not undergo the Diels–Alder reaction. Acetylation gives **6** in quantitative yield. Only traces of 2:1 adducts can be obtained in the ene reaction, even when excess paraformaldehyde and Me_2AlCl are used. Presumably electron withdrawal by the aluminum alkoxide deactivates the double bond of **5** so that the methyl group of Me_2AlCl simply adds to formaldehyde.

Treatment of **6** (25 mmol) with 3 equiv of CH_2O and 4.5 equiv of $EtAlCl_2$ in 1:1 nitromethane–methylene chloride for 12 h at 25 °C gives a 35–40% yield of **11** and ≈2% of the undesired



11, R_1=CH_2OH, R_2=Ac
12, R_1=CHO, R_2=Ac
13, R_1=$CHCH_3OH$, R_2=H
14, R_1=$COCH_3$, R_2=$SiPh_2$



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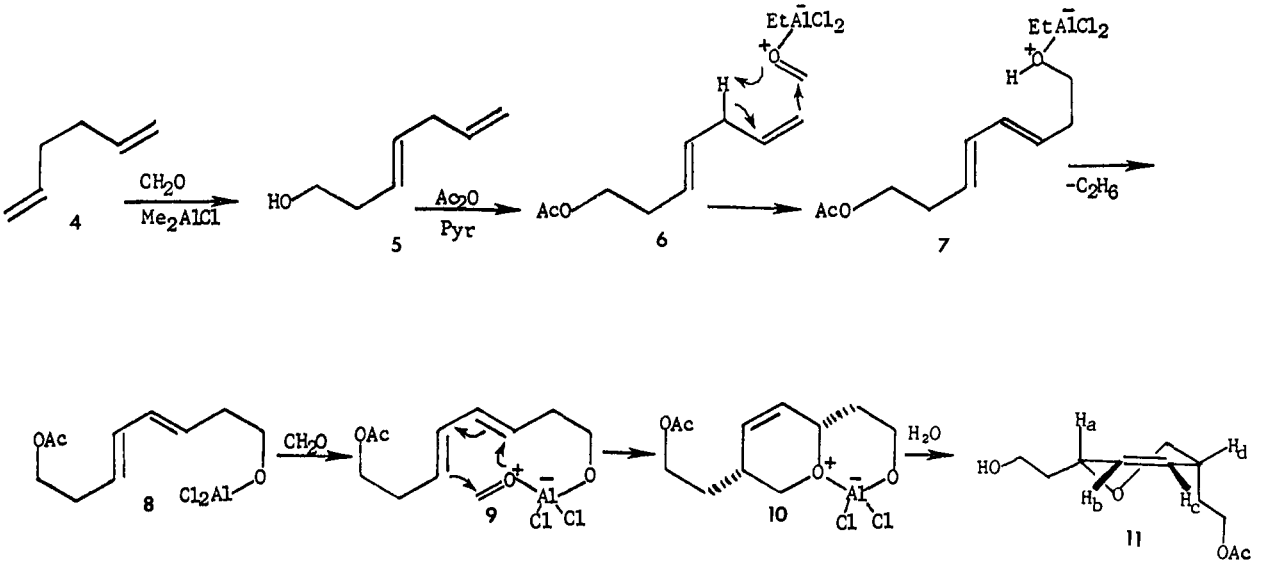
Scheme II



regioisomer as determined by analysis of the ^{13}C NMR spectrum.[10] The acetate of **6** is more basic than formaldehyde and complexes to $EtAlCl_2$. This complex reacts with CH_2O·$EtAlCl_2$ at the terminal double bond to give the ene adduct **7**, presumably as a 4:1 trans–cis mixture, which loses ethane to give **8**. This then complexes to CH_2O to give **9**, which undergoes a quasi-intramolecular Lewis acid catalyzed Diels–Alder reaction to give **10**. Aqueous workup gives **11**. Deactivation of **6** by complexation of Lewis acid to the acetate necessitates the use of $EtAlCl_2$, which is a stronger Lewis acid than Me_2AlCl with a less nucleophilic alkyl group.

The structure of **11** is assigned based on spectroscopic evidence and its conversion to **15**. The cis stereochemistry, which is expected for the Diels–Alder adduct from a trans,trans diene, can be assigned from the coupling constants of the vinylic protons.[11] H_b is weakly coupled to the vicinal pseudoaxial proton H_a (≈1 Hz) and to the allylic pseudoequatorial proton H_d (≈1 Hz). Conversely, H_c is strongly coupled to the vicinal pseudoequatorial proton H_d (5 Hz) and to the allylic pseudoaxial proton H_a (2 Hz). If the substituents were trans, H_a and H_d would both be pseudoaxial and the coupling constants of the two vinylic hydrogens would be similar.

The regiochemistry of **11** is established by NMR decoupling experiments on the aldehyde **12**. Irradiation of the allylic proton α to the oxygen at δ 4.5 collapses the signal from the methylene group α to the aldehyde at δ 2.51 to a broad singlet. The regioselectivity of the reaction depends critically on the solvent. Reaction in methylene chloride gives a 3:1 mixture of **11** and the undesired regioisomer which give a single diol after hydrolysis.

Oxidation of **11** (pyridinium CrO_3Cl, NaOAc) gives the aldehyde **12** in 87% yield. Addition of crude **12** to excess methylmagnesium chloride gives the diol **13**. Selective silylation of the primary alcohol (t-$BuPh_2SiCl$, NEt_3, $Me_2NC_5H_4N$)[12] followed by oxidation of the secondary alcohol (pyridinium CrO_3Cl) gives the methyl ketone **14** in 60% yield from **12**. Cis hydroxylation from the less hindered side (cat. OsO_4, N-methylmorpholine N-oxide)[13] followed by protection of the diol as the cyclohexylidene ketal ($C_6H_{10}O$, TsOH, $CuSO_4$) gives **15** in 82% yield (13% from 1,5-hexadiene). This material is identical with an authentic sample, kindly provided by Professor Kozikowski, by spectral and chromatographic comparison.[7] Since **15** has been converted to pseudomonic acids A[7b] and C[7a] by Kozikowski, Schmiesing, and Sorgi, this constitutes a formal total synthesis of these antibiotics.

The synthesis of **11** in three steps from 1,5-hexadiene demonstrates the utility of alkylaluminum halide catalyzed reactions of aldehydes and quasi-intramolecular Diels–Alder reactions in organic synthesis.

Acknowledgment. We thank the National Insitutes of Health and the Mobil Foundation for financial support and David J. Rodini for conducting preliminary experiments.

Registry No. (±)-**1**, 80558-54-9; **4**, 592-42-7; (*E*)-**5**, 80502-28-9; (*Z*)-**5**, 80502-29-0; **6**, 80502-30-3; **7**, 80502-31-4; **8**, 80502-32-5; (±)-**11**, 80502-33-6; (±)-**12**, 80514-57-4; (±)-**13**, 80502-34-7; (±)-**14**, 80502-35-8; (±)-**15**, 80558-55-0; (±)-pseudomonic acid C, 80558-56-1.

(10) All new compounds gave satisfactory spectral and analytical data.
(11) The conformation shown for **11** minimizes 1,3-diaxial interactions. In cyclohexenes, the vicinal coupling constant of the vinylic proton is larger for a pseudoequatorial proton which has a dihedral angle closer to the optimal 0°. The allylic coupling constant is larger for the pseudoaxial proton which has a dihedral angle closer to the optimal 90°. See: Abraham, R. J.; Gottschalk, H.; Paulsen, H.; Thomas, W. A. *J. Chem. Soc.* **1965**, 6268.
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Stereoselective Synthesis of Calonectrin

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Several macrocyclic lactones of the trichothecene class of compounds exhibit significant anticancer activity.[1] A common structural subunit in each of these lactones is the sesquiterpene verrucarol (**1**). Anguidin (**2**), a more highly oxygenated analogue, also shows inhibitory activity against several cancers.[2] Calonectrin (**3**), considered to be the biogenetic precursor to verrucarol,[3] has recently been isolated.

Several synthetic approaches to this interesting class of molecules have been reported.[4] Among these are two total syntheses

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