Actinobolin via the Anomeric Effect[1]

Md Abdur Rahman and Bert Fraser-Reid*

*Paul M. Gross Chemical Laboratory, Duke University
Durham, North Carolina 27706*

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Actinobolin (**1a**), isolated by Haskell and Bartz[2] in 1959 from cultures of *Streptomyces griseoviridies* var. *atrofacienes*, found little favor as an antibiotic, one reason being the fact that it was not readily absorbed through the stomach walls. This demerit, coupled with the subsequent discovery that the antibiotic hardens enamel,[3] has caused a reawakening of interest in actinobolin as a cariostatic agent. The discovery, 20 years later, of the antitumor agent bactobolin,[4] structurally related although not a congenor, has enhanced interest in these isocoumarins.[5] An elegant synthesis of (+)-**1**, based on an intramolecular Diels–Alder strategy, was recently reported by Ohno and co-workers.[6] In this paper, we report an alternative route to *N*-acetyldesalanylactinobolin [(+)-**1b**] (Scheme I).

The structural elucidation of **1a** was a tour de force for Munk and Haskell.[7,8] X-ray[9] and ¹H NMR[7,8] data indicated that the molecule exists in conformation **1d**, a fact that manifests itself in the ease with which the C-9 and C-10 hydroxyls can be acetonated.[8,10] For purposes of synthetic strategy, this glycol residue would have been easier to deal with if it were trans diaxial, as in the unpopulated conformer **1e**, since an epoxide, for example, Ia, would then be a logical synthon. Our recent studies on *annulated pyranosides*[12] have shown that systems such as Ia conform to the dictates of the anomeric effect,[13] even in the face of multiple

nonbonded interactions. This propensity would be severely taxed by the formidable task of favoring conformation Ia (poised for nucleophilic attack at C-9) over Ib (which would lead to the "wrong" diaxial diol because of preferential cleavage at C-10) and secondly by the need to immobilize the olefinic precursor in conformation IIa so that the erected C-4 substituent would, by steric hindrance, augment the preference for epoxidation from the convex face of this oxa-*cis*-decalin surface.

A crucial element of our synthetic strategy grew out of the discovery that the masked α-enone moiety in Danishefsky diene Diels–Alder adducts[14] can be unveiled by treatment with lithium aluminum hydride.[15] With this in mind, enone **2**[16] was converted into the adduct **3a**[17] and thence to oxime **3b** in virtually quantitative yields. Reduction of the latter with lithium aluminum hydride followed by acetic anhydride quench led to a 4:1 mixture of enone **4a**[17] and alcohol **4b**, the latter being convertible into the former by manganese dioxide oxidation.[15] The configuration at C-4 of **4** follows from our earlier studies on analogous systems[12,15] (Scheme II).

Enone **4a** presented on opportune stage at which to introduce the C-7 oxygen of actinobolin. Lead tetraacetate proved to be the reagent of choice for this α-oxygenation,[18] even though the product **5**[17] was contaminated with approximately 10% of the regioisomeric α-acetoxy ketone. Having served its purpose, the C-8 carbonyl now had to be removed, but because conventional direct methods failed,[19] a circuitous path had to be followed. Sodium borohydride reduction led to an acetoxy alcohol which was not **6a** since it failed to regenerate **5** upon treatment with manganese dioxide. Acyl migration[20] had evidently occurred leading to the regioisomer **6b**.[21]

Palladium-catalyzed deoxygenation[22] of the allylic acetate **6b** failed; however, the carbonate **7**,[17] which incidentally served to establish the C-7,C-8 stereochemistry, led to **8**[17] smoothly under the recently prescribed conditions of Sutherland.[23] Reaction of **8** with MCPBA afforded compound **9a**, and the fact that the molecule did indeed have the conformation shown was evident from the fact that $J_{1,2}$ remained ~1 Hz. The prospect for the desired trans-diaxial opening of the epoxide therefore seemed bright.

It was necessary to protect the alcohol of **9a**[17] so that it could be readily released for the future oxidation. However, cleavage of the epoxide proved to be strangely dependent upon the protecting group used. Thus, acetolysis left the benzyl ether **9b** unaffected. Fortunately the α-ethoxyethyl derivative **9c** yielded a single product.

That the oxirane had indeed been opened at C-9 of **9c** to give the desired product **10a**[17] (rather than at C-10 of **9d** which would have given the wrong diaxial isomer) was evident from two pieces

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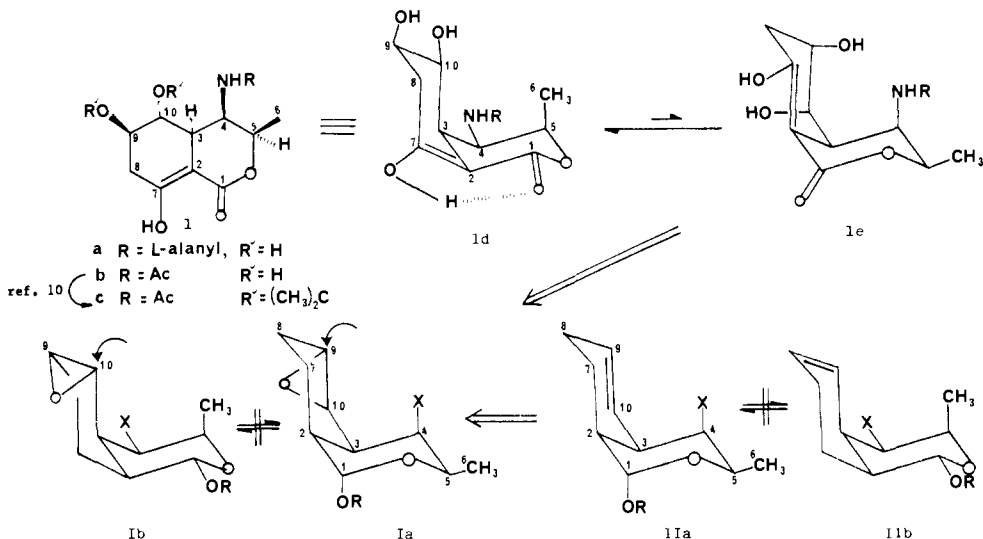
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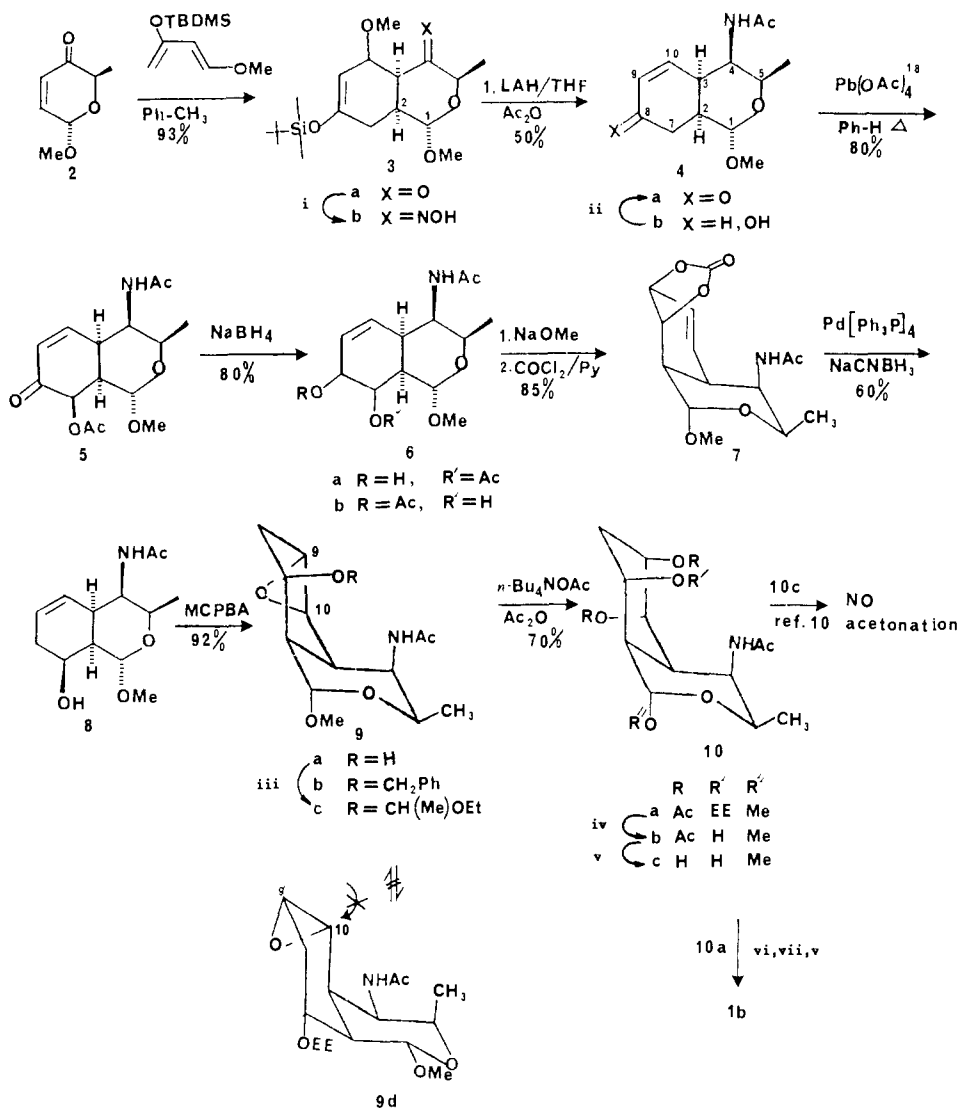(23) Sutherland, J. K.; Tometzki, G. B. *Tetrahedron Lett.* **1984,** 881.

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Scheme I[a]

[a] Sugar numbering is used throughout.

Scheme II[a]

[a] (i) NaOAc/H$_2$NOH·HCl/MeOH (90%); (ii) MnO$_2$/CH$_2$Cl$_2$ (95%); (iii) PPTs/CH$_2$CHOEt (95%); (iv) PPTS/MeOH (95%); (v) NaOMe/MeOH (90%); (vi) 2% H$_2$SO$_4$/dioxane/50 °C (42%); (vii) Me$_2$SO/TFA/TFA^{24} (70%).

of data from the 250-MHz ^{1}H NMR spectrum, (i) $J_{1,2}$ = < 1 Hz and (ii) $J_{9,10}$ = 5 Hz, which showed that both sets of protons are in the trans-diequatorial relationship. *By corollary, the latter datum shows that in spite of its heavy freight of axial substituents*

(*those at C-4 and C-7 actually being in physical contact*) the annulated pyranoside **10** resides in the conformation which enjoys the anomeric effect. In keeping with this circumstance, the diol **10c** fails to give an acetonide[8] after prolonged exposure to the conditions[10] that succeed when applied to **1b**.

Hydrolysis of the glycoside of **10a** followed by oxidation and de-O-acetylation afforded *N*-acetyldesalanylactinobolin (**1b**), identical with the sample prepared from the natural compound.[25]

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Supplementary Material Available: Proton NMR spectra, melting points, and electronic absorption spectra of compounds **1b**, **4a**, **5**, **6b**, **7**, **8**, **9a**, and **10b** and the transformation intermediates leading from **10b** to **1b** (5 pages). Ordering information is given on any current masthead page.

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(25) The details of these transformations will be published elsewhere.

H/D Exchange and Addition in the Reaction of (η⁴-C₄H₆)Fe(CO)⁻· with D₂. An Anionic Model for Homogeneous Hydrogenation

Richard N. McDonald,* Philip L. Schell, and
A. Kasem Chowdhury

*Department of Chemistry, Kansas State University
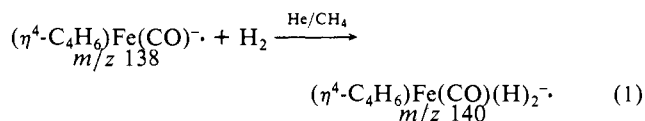Manhattan, Kansas 66506*

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$Fe(CO)_5$, $M(CO)_6$ (M = Cr, Mo, W), and various complexes of these transition metals are efficient homogeneous olefin hydrogenation catalysts at elevated temperature and high H_2 pressure.[1,2a] Thermally active catalysts which effect hydrogenation at ≤25 °C and 1 atm of H_2 are produced by photolysis of these transition-metal carbonyls and several other $L_yM'(CO)_x$ (M' = Fe, Cr, Mo, W) complexes.[2,3] The proposed mechanism for such photocatalyzed olefin hydrogenations involves formation of the coordinatively unsaturated transition-metal complex as the active catalyst. This proposal is supported by numerous photochemical studies with these and related complexes dealing with the elementary reaction channels.[3] We wish to report the generation and ion–molecule reactions of (η⁴-C₄H₆)Fe(CO)⁻· with H_2 and D_2 which corroborate certain steps in catalytic hydrogenation cycles and the coordination unsaturation of the catalytically active species.

Our studies are carried out in a previously described flowing afterglow (FA) apparatus[4] at 298 K. Briefly, the ion of interest is generated in the upstream end of the flow tube in a fast flow of helium/CH₄ (99/1) buffer gas (P = 0.55 torr, $\bar{v}$ = 80 m/s). Following thermalization of these ions by collisions with the buffer gas (50 cm), H_2 or D_2 was added via an inlet port and the ion–molecule reaction occurs in the final 65 cm of the flow tube. The flow is sampled into a differentially pumped compartment (10^{-7} torr) containing a quadrupole mass spectrometer which monitors the ion composition of the flow. The bimolecular ion–molecule rate constants are determined under pseudo-first-order conditions,
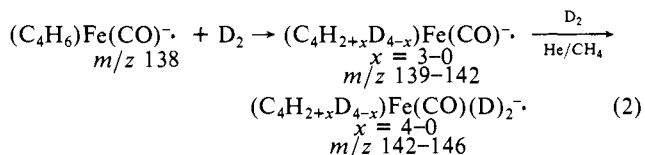
and the formation of product ions is observed directly.

When the electron gun in the FA is operated at a low emission current (EC < 50 μA), (η⁴-C₄H₆)Fe(CO)₃ attaches a thermalized electron giving the parent anion radical (η²-C₄H₆)Fe(CO)₃⁻· (*m/z* 194) exclusively; Krusic and San Fillipo[5] characterized the parent anion radical formed in the condensed phase as the 17-electron η²-diene complex. Increasing the EC to ~3 mA[6] yields a mixture of *m/z* 194 and 166. Both *m/z* 194 and 166 react with NO giving (OC)₃Fe(NO)⁻ and (OC)₂Fe(NO)⁻, respectively, by exclusive displacement of the butadiene ligand. While the ion *m/z* 194 does not react with PF₃, *m/z* 166 [(η⁴-C₄H₆)Fe(CO)₂⁻·] readily adds PF₃ termolecularly forming the adduct, most likely (η²-C₄H₆)-Fe(CO)₂(PF₃)⁻·. Neither *m/z* 166 or 194 react with H_2 or D_2 (k ≤ 10^{-13} cm³/molecule/s). Increasing the electron gun EC to ~12 mA produced a strong signal for *m/z* 138 along with signals for *m/z* 166 and 194.[6,7] The anion *m/z* 138 (*m/z* 194 − 2CO) is considered to have the structure (η⁴-C₄H₆)Fe(CO)⁻·.[8] This 15-electron structure of *m/z* 138 is supported by the fact that *m/z* 138 rapidly adds PF₃ forming the adduct (η⁴-C₄H₆)Fe(CO)(PF₃)⁻· and undergoes ligand substitution with NO yielding (η⁴-C₄H₆)-Fe(NO)⁻ (major) and (OC)Fe(NO)⁻ (minor).

Of special significance was the observation that anion radical *m/z* 138 adds H_2 termolecularly to form the adduct (η⁴-C₄H₆)-Fe(CO)(H)₂⁻·[9] (eq 1) with an apparent bimolecular rate constant

$$(\eta^4\text{-}C_4H_6)Fe(CO)^- \cdot + H_2 \xrightarrow{He/CH_4}$$
$$\underset{m/z\ 138}{}$$

$$\underset{m/z\ 140}{(\eta^4\text{-}C_4H_6)Fe(CO)(H)_2^- \cdot} \qquad (1)$$

of 1.4 × 10^{-11} cm³/molecule/s. The reaction of *m/z* 138 with D_2 occurred at twice the apparent bimolecular rate for the reaction with H_2 and revealed that up to four H/D exchanges in the diene ligand took place sequentially and competitive with adduct formation (eq 2). The results of three data points in the kinetic/

$$\underset{m/z\ 138}{(C_4H_6)Fe(CO)^- \cdot} + D_2 \rightarrow \underset{\substack{x\ =\ 3-0 \\ m/z\ 139-142}}{(C_4H_{2+x}D_{4-x})Fe(CO)^- \cdot} \xrightarrow{\underset{He/CH_4}{D_2}}$$
$$\underset{\substack{x\ =\ 4-0 \\ m/z\ 142-146}}{(C_4H_{2+x}D_{4-x})Fe(CO)(D)_2^- \cdot} \qquad (2)$$

product study of this reaction are given in Table I. Although the data for the 5% decay of *m/z* 138 with D_2 will have the largest errors, they show that the primary processes are competitive bimolecular H/D exchange and termolecular addition of D_2. The data for the first two points establish that the contribution of (η⁴-C₄H₂D₄)Fe(CO)⁻· to the *m/z* 142 signal is negligible since the *m/z* 141 ion is only just beginning to appear at 28% decay of *m/z* 138. At larger concentrations of added D_2, the isotopmer of four H/D exchanges will contribute to the *m/z* 142 signal. No signals for adducts involving five (*m/z* 147) or six (*m/z* 148) H/D exchanges were observed when sufficient D_2 was added to eliminate the ion signals at *m/z* 139–141. The kinetic data suggest that a barrier exists in forming the excited adduct **2**,[10] and the product data suggest that the rate of intramolecular H/D exchange in the diene ligand is relatively fast.

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