Total Synthesis of (±)-Ovalicin

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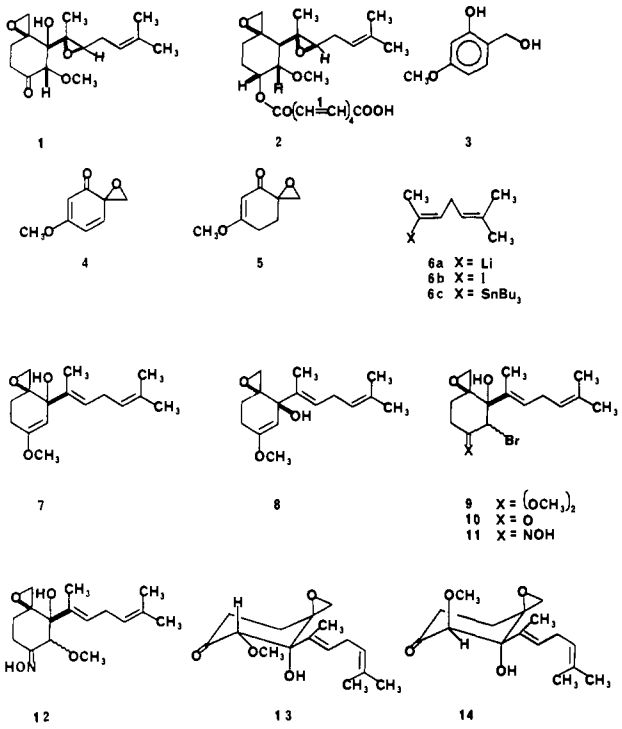
Received October 1, 1984

Ovalicin (**1**), a sesquiterpene isolated from cultures of the fungus *Pseudorotium ovalis* Stolk,[1] exhibits antibiotic, antitumor, and immunosupressive activity and, in consequence, has been the subject of extensive biochemical investigation.[2] Structurally, ovalicin (**1**) is very similar to the antibiotic fumagillin (**2**), which has been synthesized previously in these laboratories.[3] We report herein a short, stereocontrolled synthesis of ovalicin which utilizes a totally different strategy from that applied to fumagillin and which demonstrates new synthetic methodology.



Phenol **3** was prepared from 2,4-dihydroxybenzoic acid by (1) reaction with 2.5 equiv of methyl iodide and 2 equiv of potassium carbonate in acetone at reflux for 16 h to give after extractive isolation and chromatography on silica gel (sg) methyl 2-hydroxy-4-methoxybenzoate (83%) and (2) subsequent reduction with 1.8 equiv of sodium bis(2-methoxyethoxy)aluminum dihydride in ether at reflux for 30 min (97% yield). Reaction of **3** with aqueous sodium periodate solution[4] (0.3 M) in tetrahydrofuran (THF) at 23 °C for 1.5 h afforded after extractive isolation and filtration through neutral alumina (1:1 hexane–ethyl acetate) dienone epoxide **4** in 61% yield. Attempted reduction of the γ,δ double bond of **4** by catalytic hydrogenation under a wide variety of conditions resulted in formation of the phenol **3**. However, reduction using diimide[5] generated by addition of acetic acid solution (1 M in dimethoxyethane (DME) 12 equiv) over a 24 h period to a stirred mixture of **4** and potassium azodicarboxylate (18 equiv) at 45 °C in DME gave after filtration and chromatography on neutral alumina (1:1 hexane–ethyl acetate) the desired epoxy enone **5** (77%).

Vinyllithium reagent **6a** was prepared stereospecifically from vinyl iodide **6b** which was synthesized by a new method in 90% overall yield from acetone (2,4,6-triisopropylbenzyl)sulfonylhydrazone as follows.[8] To a solution of this hydrazone in DME at −78 °C was added *n*-butyllithium (2.15 equiv). The mixture was warmed to −66 °C over 20 min and recooled to −78 °C after which 1-bromo-3-methyl-2-butene (1.2 equiv) was added. The solution was warmed to −66 °C over 20 min, stirred for 1 h at −66 °C and recooled to −78 °C. Following addition of *N,N,N',N'*-tetramethylethylenediamine (3.3 equiv) and *n*-butyllithium (1.1 equiv), the reaction mixture was warmed to −3 °C over 2 h, recooled to −78 °C and treated with tri-*n*-butyltin chloride (1.25 equiv) at −78 °C for 35 min, at −35 °C for 1 h, and finally at room temperature for 45 min. Extractive isolation and chromatography on triethylamine deactivated sg (hexane eluent) gave **6c** as a single isomer with a small amount of tetra-*n*-butyltin side product (>90% purity by ^{1}H NMR analysis). Vinyltin **6c** was treated with iodine (1.2 equiv) at room temperature in methylene chloride for 1 h to afford, after extractive workup and chromatography on sg (pentane eluent), **6b**.

A solution of **6b** in ether at −78 °C was stirred with *tert*-butyllithium (1.6 equiv) for 3.25 h and then epoxy enone **5** (0.8 equiv) in toluene was added to the resulting vinyllithium reagent **6a**. After stirring at −78 °C for 1.25 h and extractive workup a 17:1 mixture (by ^{1}H NMR analysis) of diastereoisomers **7** and **8** (sg TLC R_f values 0.58 and 0.72, respectively, with 1:1 hexane–ethyl acetate) was isolated. Separation of the mixture was achieved on triethylamine deactivated sg (4:1 hexane–ethyl acetate containing 1% triethylamine cosolvent) to give pure **7** in 83% yield.

Reaction of **7** with *N*-bromosuccinimide (1.12 equiv) in methanol at 0 °C cleanly provided a 3:1 mixture (by ^{1}H NMR analysis) of bromo ketal **9** and the corresponding α-bromo α'-enol ether (sg TLC R_f values 0.33 and 0.44, respectively, with 4:1 hexane–ethyl acetate) in quantitative yield. The mixture was stirred at room temperature in acetone–water (1.5:1) with a catalytic amount of *p*-toluenesulfonic acid for 24 h to afford, after extractive workup, bromo ketone **10** (94%) which was of good purity by ^{1}H NMR analysis. Chromatography on sg at 4 °C (4:1 hexane–ethyl acetate) gave pure **10** (55% overall from **7**).

Reaction of bromo ketone **10** with hydroxylamine hydrochloride (3.56 equiv) in acetic acid buffered to pH 6 with potassium acetate (11 equiv) at room temperature for 1 h gave, after extractive workup, bromo oxime **11** (quantitative). Treatment of **11** in methanol with triethylamine (5 equiv) for 2 h at room temperature and 24 h at 48 °C yielded, after extractive isolation, the α-methoxy oxime **12** (quantitative recovery, >90% purity by ^{1}H NMR analysis). Hydrolysis of the oxime was carried out with aqueous titanium trichloride solution (4 equiv) in methanol buffered with aqueous ammonium acetate solution (pH 6; 18 equiv) for 2.5 h at room temperature[9] to provide, after extractive isolation, a 1:1 mixture of diastereoisomers **13** and **14**. Treatment of the mixture with potassium carbonate (2 equiv) in methanol at 0 °C for 2 h resulted in complete isomerization of **14** to **13**, which was isolated in pure condition (63% from **12**) by chromatography on triethylamine-deactivated sg (3:1 hexane–ethyl acetate). The conversion of **13** to ovalicin (**1**) was carried out as follows. A solution of **13** in benzene was treated with vanadyl acetylacetonate (0.14

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equiv)[10] followed by a solution of dry *tert*-butyl hydroperoxide in toluene (2 equiv) for 2 h at room temperature to give stereospecifically (by TLC and ^{1}H NMR analyses) (±)-ovalicin (**1**), which was isolated by chromatography on triethylamine-deactivated sg (3:1 hexane–ethyl acetate) in 89% yield. Synthetic (±)-**1** was indistinguishable from an authentic sample by ^{1}H NMR, IR, mass spectra, ^{13}C NMR analyses as well as chromatographic mobility on sg in several solvent systems.

The method outlined above for the synthesis of 1,4-dienes **6a** and **6b** represents a new approach to trisubstituted olefins which should be widely useful because it is simple, C–C connective, and stereospecific. It demonstrates a previously unrecognized property of the Shapiro reaction to produce the *E*-trisubstituted azenolate geometry which then can be translated into *E*-trisubstituted olefins such as **6**. The novel synthesis of epoxy ketone **5**, the highly stereoselective conversion of **5** to **7**, and the stereospecific, internally directed epoxidation of **13** to ovalicin are also noteworthy.[11]

Supplementary Material Available: Spectroscopic data (PMR, ^{13}C NMR, IR, and mass spectral) are provided for compounds **3–5**, **6b,c** **7–9**, α-bromo α′-methyl enol ether of **10**, **10–13**, and (±)-**1** (synthetic) (3 pages). Ordering information is given on any current masthead page.

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(11) This research was supported by grants from the National Institutes of Health and the National Science Foundation. We are grateful to Drs. H. P. Sigg and P. Bollinger of the Sandoz Co., Basel, Switzerland for a sample of ovalicin.

Electronic Structure of the $MoFe_3S_4(SH)_6^{3-}$ Ion†

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Received June 18, 1984

Recently several single- and double-cube compounds containing the cubane-type $[MoFe_3S_4]^{3+}$ core cluster have been synthesized.[1-6] The single-cube $MoFe_3S_4$ cluster is of particular interest because of its possible relation to the FeMo cofactor of nitrogenase[1,4] and its structural similarity to the $[Fe_4S_4]^{2+}$ site of oxidized ferredoxins. In this paper we report results of MS–Xα calculations on the hypothetical $MoFe_3S_4(SH)_6^{3-}$ cluster, a 289-electron system, and compare them with experimental data and with the Fe_4S_4 cluster calculations of Aizman and Case.[7] Figure 1 illustrates the structure used in the calculations. In the Xα method, both spin-restricted (same spatial orbitals for α and β spin) and spin-unrestricted calculations (different spatial orbitals for different spins) can be performed. While the former are simpler to interpret in ligand-field terms, an unrestricted treatment generally yields more satisfactory results for open-shell systems; the calculations we report here are all spin unrestricted.

Single-cube $MoFe_3S_4$ clusters are found experimentally to have quartet spin ($S = {}^3/_2$).[4] In C_{3v} symmetry the lowest energy quartet Xα configuration (Figure 2) is $[\cdots(16e^{\alpha})^2(16e^{\beta})^2(4a_2^{\alpha})^1(17e^{\alpha})^2]$. This quartet is not, however, the Xα ground state. Two occupied

†Supported in part by a grant from the National Science Foundation.

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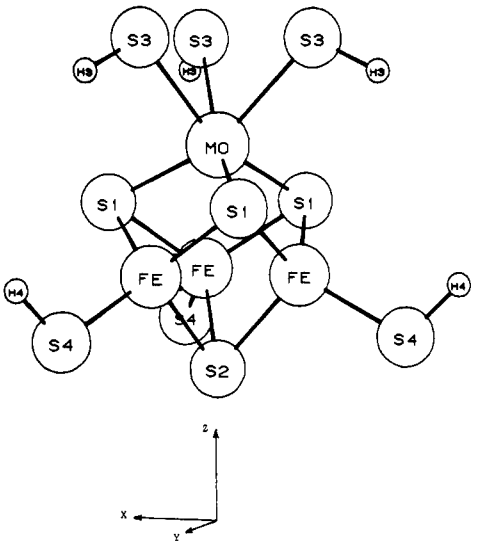

Figure 1. ORTEP drawing of the model $MoFe_3S_4(SH)_6^{3-}$ cluster. This C_{3v} model geometry is based on averaged interatomic distances and bond angles of the core from the crystal structure[6] of $Mo_2Fe_6S_8(SEt)_9^{3-}$; all the single- and double-cube clusters have very similar core geometries. The cartesian axes show the orientation of the molecule in the coordinate system. In units of a_0, the (x, z) coordinates of the atoms lying in the xz plane are as follows: Mo (0.0, 2.3619), Fe (-2.9316, -1.8670), S1 (4.0008, 0.4302), S2 (0.0, -5.0061), S3 (-3.3942, 5.8276), S4 (-6.6850, -3.7913), H3 (-5.6926, 4.7848), H4 (-8.5351, -2.0745). Out-of-plane atomic coordinates are related to these by ±120° rotations about the z axis.

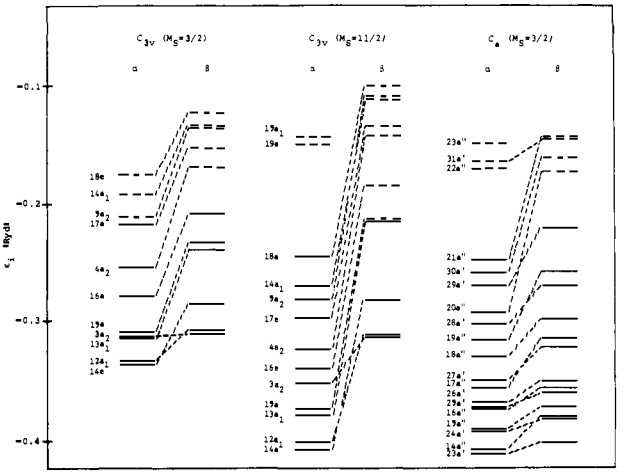

Figure 2. One-electron energy level diagrams for the different states of the $MoFe_3S_4(SH)_6^{3-}$ cluster; only the energy levels near the highest occupied orbital are shown. Occupied spin oribtals are denoted by solid horizontal lines, virtual levels by broken lines. Each α-spin orbital is connected to the corresponding β-spin level by a dashed line.

$16e^{\beta}$ spin orbitals (-0.207 Ry) lie above an unoccupied $5a_2^{\alpha}$ level (-0.209 Ry). Flipping the spin of one of the high-energy β electrons and transferring it to $5a_2^{\alpha}$ decreases the total energy, while lowering additional unoccupied α-spin levels below occupied β-spin levels. This self-reinforcing process continues until an $M_S = {}^{11}/_2$ state is reached in which all the occupied levels lie below the virtual levels (Figure 2). The configuration is $[\cdots(13a_1^{\alpha})^1(13a_1^{\beta})^1(15e^{\alpha})^2(16e^{\alpha})^2(4a_2^{\alpha})^1(17e^{\alpha})^2(5a_2^{\alpha})^1(14a_1^{\alpha})^1(18e^{\alpha})^2]$, and the state energy is 1.32 eV below that of the quartet.

This $M_S = {}^{11}/_2$ configuration is the Xα ground state in C_{3v} symmetry, but it is necessary to investigate whether a determinant of reduced symmetry can yield an even lower energy. Such spatial instabilities are well-known in Hartree–Fock[8-10] and Xα[11-14]

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