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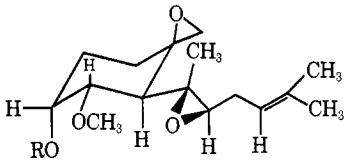
A Total Synthesis of (±)-Fumagillin

Sir:

Fumagillin is an antibiotic isolated from *Aspergillus fumigatus* with antiparasitic[1] and carcinolytic[2] activity. Chemical degradation[3] and X-ray crystallographic[4] studies have led to the assignment of structure **1** to

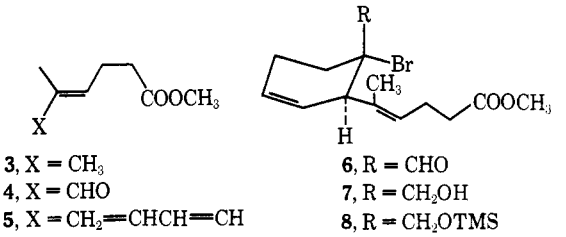


1, R = CO(CH=CH)$_4$COOH
2, R = H

fumagillin. The biological activity and novel structure of fumagillin have stimulated the interest of several groups in synthesis. However, the complications of asymmetry (six centers) and highly reactive functionality have conspired to prevent solution of the problem.[5]

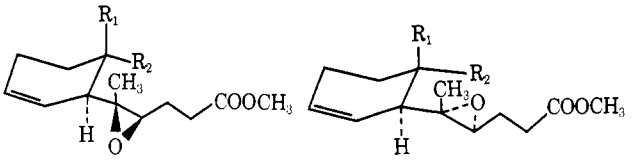
The goal of this synthesis was (±)-fumagillol (**2**), since this should be easily convertible to fumagillin. In fact, treatment of (−)-fumagillol, readily available by degradation of fumagillin,[6] with 1 equiv of methyllithium, followed by addition of this solution to 5 equiv of decatetraenedioyl chloride in tetrahydrofuran at −78°, gave fumagillin, identical with natural fumagillin by thin-layer chromatographic (tlc), infrared (ir), nuclear magnetic resonance (nmr), and mass spectral comparison.

The demonstration of the first total synthesis of (±)-fumagillol proceeded as follows. Alkylation of methyl acetoacetate with 3,3-dimethylallyl bromide[7] followed by deacetylation using the procedure of Ritter and Kaniecki[8] gave methyl 5-methyl-4-hexenoate (**3**),[9] bp 47–50° (5 mm) (57% yield). Oxidation of the olefin **3** with selenium dioxide in 97% aqueous 1,2-dimethoxyethane for 8 hr at reflux gave stereoselectively in 41% yield the α,β-unsaturated aldehyde **4**[10,11] [ir max (neat) 5.73, 5.91, 6.10 μ; nmr peaks due to CHO (δ 9.41), HC=C (6.5, br), and CH_3C=C (1.80)], which was converted into the triene **5** in 84% yield by reaction with allylidenetriphenylphosphorane in tetrahydrofuran (−25° for 30 min and 25° for 2 hr)[11] [found for **5**: ir max (neat) 5.72, 6.15 μ; uv max (cyclohexane) 245 (14,000), 255 (23,000), 265 (28,000), and 276 (21,000) nm].



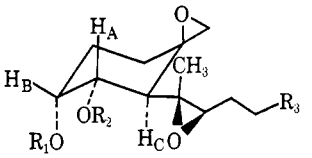
3, X = CH_3
4, X = CHO
5, X = CH_2=CHCH=CH

6, R = CHO
7, R = CH_2OH
8, R = CH_2OTMS

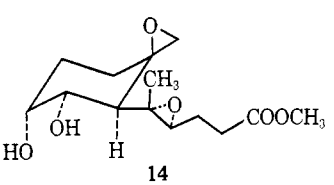


9, R_1 = CH_2OTMS; R_2 = Br
11, R_1 = R_2 = $-OCH_2$

10, R_1 = CH_2OTMS; R_2 = Br
12, R_1, R_2 = OCH_2



13, R_1 = R_2 = H; R_3 = $COOCH_3$
15, R_1 = H; R_2 = CH_3; R_3 = $COOCH_3$
16, R_1 = H; R_2 = CH_3; R_3 = $C(CH_3)_2OH$
17, R_1 = $COCH_3$; R_2 = CH_3; R_3 = $C(CH_3)_2OH$



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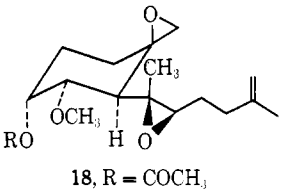

18, R = $COCH_3$
19, R = H

Nmr analysis indicated the triene **5** to be a 1:1 mixture of cis and trans isomers (peaks due to CH_3C=C at δ 1.83 and 1.78) differing about the central double bond, which isomerized rapidly at 80° to a mixture containing greater than 95% of the trans form. Reaction of **5** with 1.3 equiv of α-bromoacrolein at reflux in benzene containing potassium carbonate and hydroquinone for 48 hr gave a high yield of Diels–Alder product consisting mainly (80%) of the desired adduct **6**[12] [ir max (neat) 5.72 and 5.78 μ; nmr peaks at δ 9.45 (CHO, 1 H) and 1.55 (CH_3C=C, 3 H)] and two minor components of unassigned structure (CHO proton resonance at δ 9.36 and 9.29). Reduction of this mixture with sodium borohydride in wet tetrahydrofuran gave

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(9) Satisfactory nmr, ir, and mass spectra were obtained for all intermediates.

(10) The stereochemistry of selenium dioxide oxidation of similar compounds has been examined previously; see U. T. Bhalerao and H. Rapoport, *J. Amer. Chem. Soc.*, **93**, 4835 (1971), and references contained therein.

(11) Elemental analysis or high-resolution mass spectral data for this compound are in accord with theory.

(12) The assignment of structure **6** rests on the eventual conversion of this material to (±)-fumagillol.

(>98%) crude alcohol **7** which was converted to the corresponding trimethylsilyl ether **8** by treatment with trimethylsilyl chloride–triethylamine for 8 hr at 25° in tetrahydrofuran (90% yield). Epoxidation of **8** with 1 equiv of *m*-chloroperbenzoic acid in methylene chloride at 0° containing sodium bicarbonate as an acid acceptor gave in 80% yield a mixture of **9** and **10** with the desired isomer **9** predominating by 9:1 as determined by nmr signals due to oxirane methyl at 1.21 and 1.24, respectively. The stereoselectivity of the epoxidation process was anticipated on the basis that the most stable conformation of the six-carbon side chain in **8** is as shown (see ref 4a) and the strong steric shielding at one face of the trisubstituted double bond by the silyloxy and bromine ring substituents. Attempted hydrolysis of the silyl ether linkage under the usual conditions in protic solvents (potassium carbonate in methanol; ammonium chloride in tetrahydrofuran–water; ammonium chloride in methanol–water) led to rapid attack on the epoxide ring by the liberated primary hydroxyl group, presumably giving products containing a tetrahydrofuran or tetrahydropyran ring. However, hydrolysis under aprotic conditions (anhydrous tetrabutylammonium fluoride in tetrahydrofuran), followed by cyclization with sodium methoxide, gave a 9:1 mixture of **11** and **12** in high yield (nmr signals due to oxirane methyl at δ 1.29 and 1.35, respectively).[13] Hydroxylation with osmium tetroxide in pyridine gave in 81% yield a 9:1 mixture of **13** and **14**. Chromatographic separation gave pure **13**, mp 103.5–105° (31% from **5**)[11] [found for **13**: ir max ($CHCl_3$) 2.8, 5.72, 9.3 μ; nmr peaks at δ 1.26 (3 H, CH_3), 3.72 (3 H, OCH_3), and 4.1 (2 H, m, H_A and H_B)].[14]

Conversion of diol **13** to the monomethyl ether **15** was accomplished in 47% yield (65% based on recovered starting material) by treatment with 1.3 equiv of sodium *tert*-amylate in tetrahydrofuran followed by addition of excess methyl iodide. Reaction of **15** with excess methyllithium in tetrahydrofuran at −78° gave the dihydroxy diepoxide **16** (*ca.* 75% yield) [found for **16**: ir max ($CHCl_3$) 2.95 and 9.1 μ; nmr peaks at δ 1.27 (3 H, CH_3), 1.30 (6 H, CH_3) 3.52 (3 H, OCH_3), 3.63 (1 H, d of d, J_{AC} = 11 Hz, J_{AB} = 2 Hz, H_A), and 4.4 (1 H, br, H_B)], which was acetylated to afford the monoacetate **17** (95% yield) by treatment with pyridine–acetic anhydride for 24 hr at 50° [found for **17**: ir max ($CHCl_3$) 2.9, 5.72, 8.05 μ; nmr peaks at δ 1.28 (9 H, CH_3), 2.07 (3 H, CH_3), 3.40 (3 H, OCH_3), 3.58 (1 H, d of d, J_{AC} = 11 Hz, J_{AB} = 2 Hz, H_A), 5.55 (1 H, br, H_B)]. Dehydration of the alcohol **17** was effected by mesylation with mesyl chloride–triethylamine in tetrahydrofuran for 30 min at −15°[15] followed by elimination promoted by the addition of 1 equiv of tetrabutylammonium bromide in tetrahydrofuran (stirring for 3 hr at 25°) to give fumagillyl acetate as the major product and the isomer **18** as a minor product (ratio 3:1, respectively). The position selectivity in the elimination of **17** appears to be considerably less than reported[16] for a similar case (selectivity 9:1) under the same conditions. Saponification of this mixture of acetates with anhydrous potassium carbonate in methanol gave (±)-fumagillol (**2**) and its isomer **19** as a mixture which was inseparable by tlc. Separation was achieved by high-pressure liquid chromatography using a Waters Associates ALC-202 instrument (using silica gel with 4:1 methylene chloride–acetonitrile as solvent), giving pure (±)-fumagillol, mp 111–113°, identical with natural fumagillol by tlc, ir, nmr, and mass spectral comparison. This was converted to (±)-fumagillin (identical with natural material by tlc and infrared comparison) as described above.[17]

(13) The use of fluoride ion in this process was suggested by the high value of the Si–F bond energy (*ca.* 135 kcal/mol); see also, C. S. Kraihanzel and J. E. Poist, *J. Organometal. Chem.*, **8**, 239 (1967).

(14) In the nmr spectrum of **13** (and also compounds **15**–**17** and **1**) the half band widths of the four peaks due to the CH_2 of the spirooxirane ring were approximately the same as expected for equatorial orientation of that CH_2 [see L. J. T. Andrews, J. M. Coxon, and M. P. Hartshorn, *J. Org. Chem.*, **34**, 1126 (1969)].

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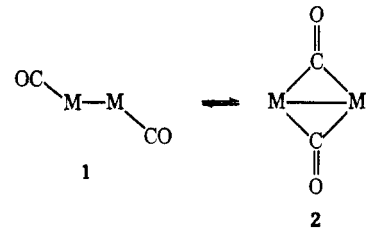
Temperature-Dependent Carbon-13 Nuclear Magnetic Resonance Spectra of the h^5-Cyclopentadienyliron Dicarbonyl Dimer, an Application of a Shiftless Relaxation Reagent

Sir:

Applications of Fourier transform (FT)[1] methods to obtain carbon-13 nmr (cmr) spectra of metal carbonyls have as yet remained largely unexploited.[2] The reason underlying this state of affairs is that metal-bonded carbonyls have long T_1 relaxation times. Consequently, small flip angles and long pauses between successive pulses in the FT experiment are required to obtain a free induction decay. If small amounts of kinetically inert, paramagnetic metal complexes with a totally symmetric ground state such as tris(acetylacetonato)-chromium(III) are added to solutions of metal carbonyls, T_1 relaxation times are drastically reduced, absolutely no contact chemical shift is detected within ±0.1 ppm, and little line broadening is observed for $Cr(acac)_3$ concentrations less that 0.10 *M*.

The utility of this shiftless relaxation reagent is demonstrated by cmr studies of $[(h^5\text{-}C_5H_5)Fe(CO)_2]$ (I) and $Fe_3(CO)_{12}$ (II). These studies prove that at least the first of these molecules undergoes bridged–nonbridged structure interconversions of the kind **1** ⇄ **2** and is



1 **2**

therefore a member of a newly found important class of stereochemically nonrigid molecules as suggested by Cotton and coworkers.[3]

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(2) L. F. Farnell, E. W. Randall, and E. Rosenberg, *Chem. Commun.*, 1078 (1971). A few chemical shifts are reported therein, but no experimental details are given.

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