1-1-1988

The application of manganese (III) acetate to the synthesis of two diverse biologically active compounds

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The Application of Manganese(III) Acetate to the Synthesis of Two Diverse Biologically Active Compounds

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Senior Honors Thesis
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Abstract:

Methyl-4-oxo-10-(1-oxoethoxy)-tricyclo[6.3.0.$0^{2,6}$]undecan-5-oate, a synthetic precursor to hirsutene, was prepared in moderate yields *via* an intramolecular radical tandem cyclization of 4-(2,6-cyclooctadienyl)methyl acetoacetate induced by manganese(III) acetate. Two analogous polysubstituted dihydrofurans of expected PAF antagonistic activity were prepared in good yields from the manganese(III) acetate induced fusion of a substituted styrene with a substituted benzoyl acetate. The use of manganese(III) acetate oxidations in the syntheses of such diverse compounds promises greater applications of this chemistry towards other synthetic problems in the future.

The following thesis is presented as partial fulfillment of requirements for graduation with University Honors.

INTRODUCTION

The synthesis of natural and unnatural products has become an area of concentrated energy and resources. The development of novel, effective methodology in the support of this field has grown quickly--necessitating the expansion of new facets of organic chemistry. One rapidly growing area is the oxidation of organic compounds by manganese(III) acetate dihydrate ($[Mn_3O]$). The oxidations allow for the formation of new carbon-carbon single bonds within a molecule or between molecules, affording the rapid, one-step synthesis of complex molecules from simple starting materials.

The oxidative chemistry of $[Mn_3O]$ towards organic compounds is based on the unstable oxidation state of manganese(III); the most stable oxidation state for manganese is +2[1]. The oxidizing strength of this system is mild; $[Mn_3O]$ will selectively remove a hydrogen radical from the most acidic site on the molecule: sites adjacent to beta-diketo or beta-ketoester functionalities[2]. The position of the resulting radical is therefore controlled *in situ* by the location of acidic sites on the cyclization precursor. The subsequent intra- or intermolecular radical reactions provide the pathway to larger, more complex molecules. The following describes two applications of $[Mn_3O]$ induced radical cyclizations to the synthesis of diverse compounds: a fused cyclopentanoid ring system (a precursor to hirsutene), and a trisubstituted dihydrofuran.

Hirsutene (Fig. 1) occurs naturally in the Chinese mushroom *Coriolus conlons*[3]. This and related compounds have shown biological

activity as antitumor and antibiotic agents[4]. The biological activity of the triquinanes has fueled the development of several synthetic routes to these compounds[5].

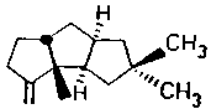
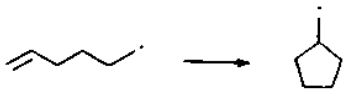


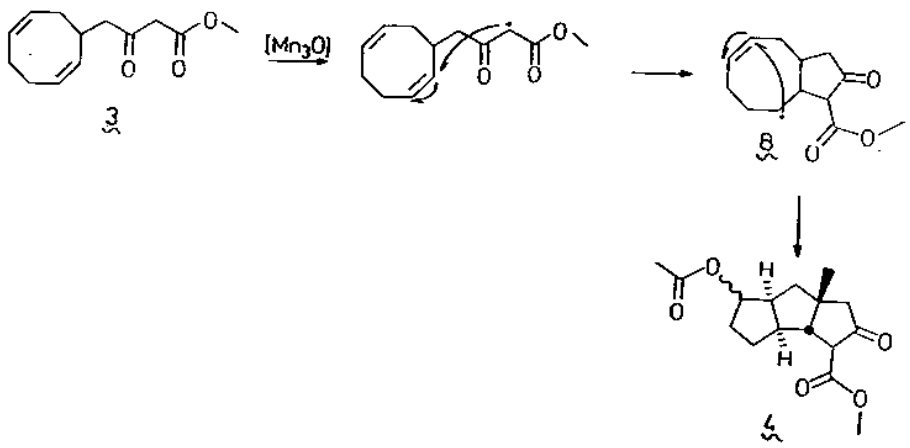
FIG. 1 Hirsutene

The tricyclopentanoidal structure of hirsutene is especially suited to the [Mn_3O] oxidation. It has been shown that the 5-hexenyl radical will cyclize into methylenecyclopentyl radical[6] (See Scheme I). The tricyclopentanoidal fused ring structure of the triquinanes would require a cyclization precursor that provides both a functionality conducive to [Mn_3O] induced radicalization (a beta-diketo or beta-ketoester moiety), and the proper structure that would yield 5-hexenyl radical configurations, allowing multiple intramolecular cyclizations to occur.

SCHEME I



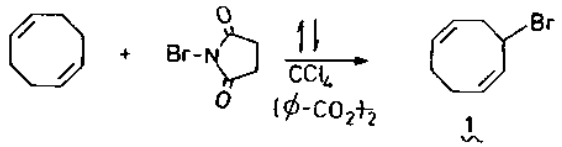
SCHEME II



4-(2,6-Cyclooctadienyl)methyl acetoacetate supplies both a site for selective generation of a radical and the correct configuration of carbon-carbon double bonds, producing 5-hexenyl radicals which will intramolecularly cyclize to a tricyclo[6.3.0.$0^{2,6}$]undecane carbon skeleton (See Scheme II). 4-(2,6-Cyclooctadienyl)methyl acetoacetate is

easily synthesized in the laboratory from readily available starting materials, making it highly feasible for use as a cyclization precursor (See Scheme III).

SCHEME III



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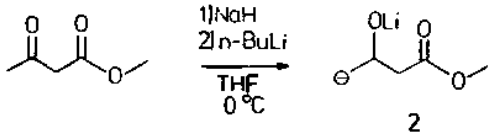


2

Several polysubstituted furanoid lignans have been found to act as platelet activating factor (PAF) antagonists in mammalian systems[7]. Compounds such as L-652,731 (3,4-dimethyl-2,5-bis(3,4,5-trimethoxyphenyl)-tetrahydrofuran) (Fig. 2), are among the most potent known PAF antagonists[8]. In addition, few synthetic products show antagonistic activity[9], making a synthetic route to these types of compounds highly desirable.

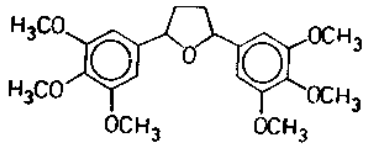
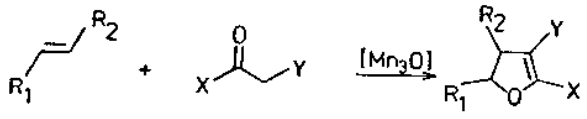


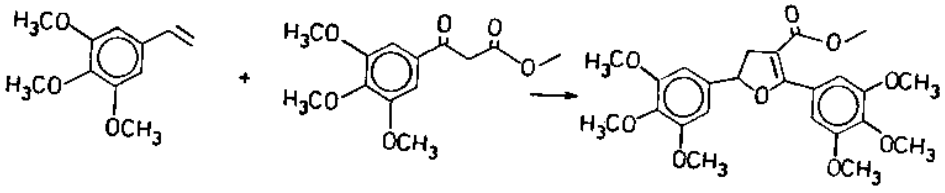
FIG. 2 L-652,731

It has been known for some time that a substituted vinyl group will fuse with a beta-diketone moiety during reaction with manganese(III) in acetic acid[10] (See Scheme IV). The product of this reaction is a substituted dihydrofuran. We would predict then that the fusion of 3,4,5-trimethoxystyrene with 3,4,5-trimethoxybenzoyl acetate produces a trimethoxyphenyl-disubstituted dihydrofuran (7), an analogous compound to L-652,731 (See Scheme V).

SCHEME IV

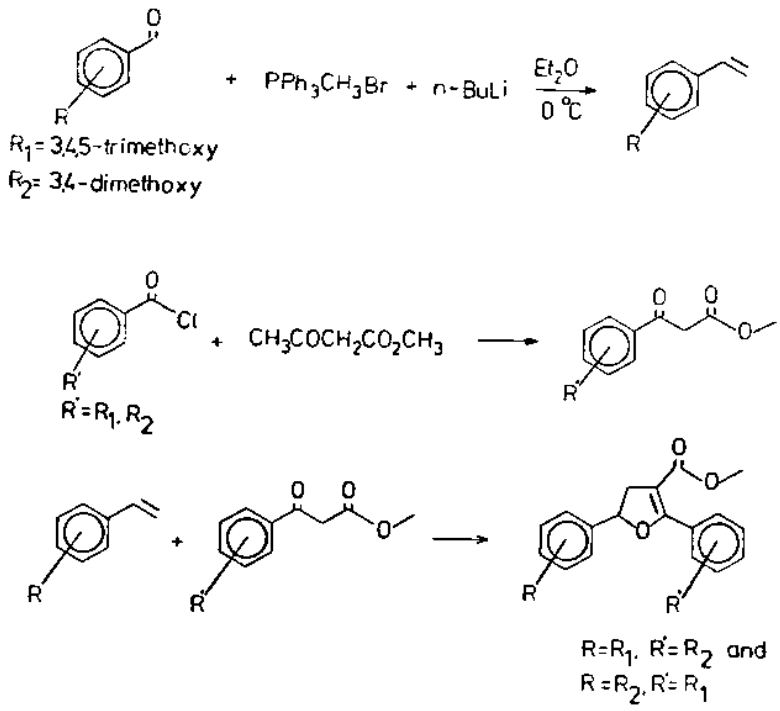


SCHEME V



The preparation of the styrene and the benzoyl acetate are both straightforward, high-yield syntheses, allowing for the rapid preparation of an array of variously substituted starting materials (See Scheme VI).

SCHEME VI



RESULTS & DISCUSSION

Triquinane:

The tricyclopentanoidal precursor to hirsutene was prepared via a [Mn_3O] induced intramolecular cyclization of 4-(2,6-cyclooctadienyl)-methyl acetoacetate (3) which was prepared as described below from 1,5-cyclooctadiene. 1,5-Cyclooctadiene is refluxed in carbon tetrachloride with N-bromosuccinimide and, benzoyl peroxide affording 1-bromocyclooctadiene (1)(60% yield). The treatment of ethyl acetoacetate with sodium hydride in THF, followed by n-butyl lithium gives the dianion (2). A solution of 1 is then added to the dianion in situ, yielding 3 (50% yield). The cyclization precursor, 3, is oxidized by [Mn_3O], cupric acetate, and potassium acetate in acetic acid, generating the tricyclopentanoidal acetate (4) (30% yield after work-up and purification). The overall yield of triquinane from cyclooctadiene is approximately 9%.

The configuration of naturally derived hirsutene is cis,anti,cis at the ring junctions (See Fig. 1). It is therefore necessary for the synthesized triquinane to possess the same structure. The intramolecular cyclization of a cyclopentyl system favors the formation of the cis- ring product. We predict then that the proper ring junction configuration will result. This will be verified by saponification and subsequent oxidation of the ester groups to carbonyls. The ^{13}C-NMR spectrum of the resulting, rigid structure can then be examined to determine the actual configuration of the molecule.

Furan:

The furanoids were prepared via manganese-induced fusion of a substituted styrene and benzoyl acetate. Our lab has prepared several analogous trisubstituted dihydrofurans by varying the number, type, and position of functionalities substituted on the starting styrene and benzoyl acetate. Two analogs were prepared as part of this project and will be reported here as examples of the general reaction.

The styrene (5) is prepared via a Wittig reaction involving the appropriately substituted benzaldehyde, methyltriphenylphosphonium bromide and n-butyl lithium (50% yield). The benzoyl acetate (6) is prepared by reacting the appropriately substituted benzoyl chloride with methyl acetoacetate in the presence of sodium hydroxide, with an ammonium chloride quench. All the benzoyl acetates were prepared and purified by T. J. Winter, and were used as received. The styrene and benzoyl acetate are reacted with [Mn_3O], cupric acetate, and potassium acetate in acetic acid to form the trisubstituted dihydrofuran (7) (60% yield, after work-up, and purification).

CONCLUSIONS

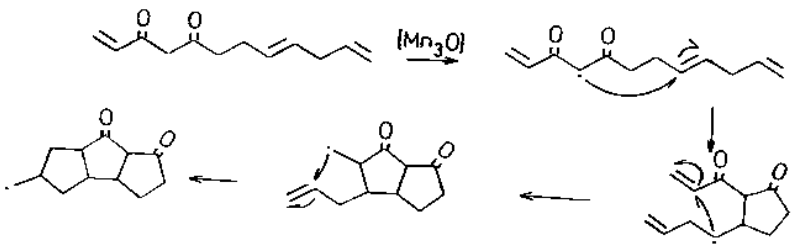
Triquinane:

The overall yields of triquinane recovered from this synthetic route have been moderate at best. Two observations provide viable explanations of this fact. First, in the purification step a large amount of the cyclization intermediate (8) was recovered, suggesting that conditions optimizing the second cyclization were not being employed. Second, a balance in mass was not observed from the

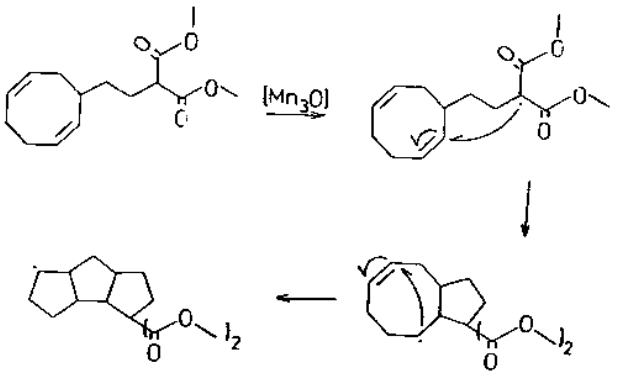
chromatography. It was observed that material would elute from the column when a highly polar solution (50% ethyl acetate (EA)/ petroleum ether (PE)) was used as a post-analysis wash. This suggests that perhaps some oxidation was occuring other than just a radicalization, or that acetic acid was being extracted as product and was affecting the product's activity towards the column. It has also been noted that these carbocycles can be very volatile[11]; perhaps some product is lost during the removal of the solvent. Future work should be directed toward optimizing the conditions for the second cyclization, and improving the work up and purification techniques.

The problem of the first cyclization being hindered has also been considered. The initial reaction after radicalization occurs by the radical attacking to the carbon-carbon double bond on the ring (See Scheme II). In doing so it pivots on the carbon alpha to the ketone, bending at the carbonyl carbon. Perhaps having to bend at an sp^2-hybridized carbon holds the radical too far from the alkene for it to be able to attack efficiently. Further study could pursue the synthesis and effects of using a cyclization precursor that has an sp^3-hybridized carbon at the bending point: either a cyclic (9, See Scheme VII), or an acyclic precursor (10, See Scheme VIII).

SCHEME VIII



SCHEME VII



Furans:

The work done in this project was focused towards investigating the effect of reacting various combinations of substituted styrenes with

benzoylacetates on the yields of trisubstituted dihydrofurans (See Scheme IV). Both furans prepared in this project were obtained in good yields (50-60%). The purification and isolation of the products proved to be straight-forward and suggests that the yields could be improved. Future studies should include the optimization of the reaction conditions, and the determination of the activity of these compounds as PAF antagonists.

EXPERIMENTAL

Infrared spectra were acquired on a Sargent Welch 3-200 spectrophotometer. Samples were prepared and analyzed either as thin films or in KBr pellets. NMR spectra were generated on an IBM WP-200 instrument at 200 MHz for proton and at 50 MHz for carbon. All spectra were interpreted in collaboration with Dr. J. R. Peterson. Products purified by Medium Pressure Liquid Chromatography (MPLC) were chromatographed on a silica gel column, equipped with an FMI pump, and detected by a Gilson Model 131 refractive index detector.

1 1-Bromo-2,6-cyclooctadiene: 1,5-Cyclooctadiene (47.0 g, 1.5 eq.), N-bromosuccinimide (53.0g, 1.0 eq.), and benzoyl peroxide (2.0 g, 0.03 eq.) are refluxed in 250 mL of CCl_4 for 3.5 hrs. The mixture is allowed to cool, and the solid succinimide is removed by vacuum filtration over a sintered glass funnel. The filtrate is washed with dilute $NaHCO_3$ (2 X 75 mL), and with H_2O (2 X 75 mL). The organic layer is collected and dried over anhydrous $MgSO_4$. The solvent is evaporated, and the resulting oil is purified by distillation (P = 1.6 torr, b.p. = 64-68 ^oC).

2 Enolate dianion of ethyl acetoacetate: 0.88 g of NaH (1.1 eq.,

60% suspension in mineral oil) is suspended with vigorous stirring in 58 mL of freshly distilled THF at 0 °C under N_2. 2.32 g of methyl acetoacetate (1.0 eq.) is then added dropwise and the mixture is allowed to stir for 10 minutes. n-Butyl lithium in hexane (11.40 mL of 1.86 M, 1.0 eq.) is added to the cold solution, and stirring is continued for 10 minutes.

3 4-(2,6-Cyclooctadienyl)methyl acetoacetate: 1-Bromo-2,6-cyclooctadiene (1)(4.00 g, 1.1 eq.) is added to the dianion (2) *in situ*. The ice bath is removed, and the mixture is allowed to stir under N_2 for 15 minutes. The reaction is quenched with a mixture of concentrated HCl (8 mL), H_2O (20 mL), and Et_2O (30 mL). The ether layer is collected, and the aqueous layer is further extracted with Et_2O (2 X 30 mL). The extracts are combined, washed with H_2O (6 X 20 mL), dried over anhydrous $MgSO_4$, and the solvent is evaporated yielding a yellow oil. The oil is purified by chromatography on a "flash" silica gel column, eluting with 15% EA/PE.

4 Tricyclopentanoidal acetate: To a 50 mL round-bottomed flask, 0.2 g of 3 (1.0 eq.) is added to 15 mL of acetic acid. 0.08 g of cupric acetate (0.5 eq.) ($Cu(CO_2CH_3)_2$), 0.36 g potassium acetate (4.0 eq.), and 0.6 g of manganese(III) acetate ($Mn(CO_2CH_3)_3\ 2H_2O$) (2.5 eq.) are added sequentially with stirring. The flask and water-cooled condenser are flushed with N_2, and set into an oil bath at 50-55 °C. The mixture is allowed to stir until the color changes to dark blue (about 20-2 mins.). The flask is then removed from the oil bath, and stirring under N_2 until it cools to room temperature. The reaction mixture is then diluted

with 10 mL of H_2O and subsequently extracted with $CHCl_3$ (6 X10 mL). The extracts are combined, washed with H_2O (3 X 10 mL) and with saturated $NaHCO_3$ solution (2 X 10 mL). The extracts are dried over anhydrous $MgSO_4$, and the solvent is evaporated. The resulting yellow oil is purified by MPLC eluting with 15% EA/PE.

5 Polysubstituted styrene: Methyltriphenylphosphonium bromide (19.1 g, 1.05 eq.) is placed in a 1000 mL round-bottomed flask with magnetic stirring bar under N_2. Anhydrous Et_2O (200 mL) is added, and the mixture is allowed to stir for 15 min. at 0 °C. n-Butyl lithium (24.9 mL of 2.15 M, 1.05 eq.) is added dropwise to the cold mixture. 10.0 g the appropriately substituted aldehyde (1.0 eq.) dissolved in 200 mL of anhydrous Et_2O is then added to the cold reaction mixture. The reaction is allowed to stir for 5-6 hr. The reaction is quenched with 190 mL of saturated, aqueous NH_4Cl solution. The layers are separated and the aqueous layer is extracted with Et_2O (2 X 80 mL). The extracts are washed with saturated, aqueous NaCl solution and dried over $MgSO_4$. The solvent is removed and the resulting oil is purified by chromatography on a silica gel column eluting with 20% EA/PE.

6 Polysubstituted benzoyl acetate: These compounds were prepared and purified by T. J. Winter, and were used as received.

7 Trisubstituted dihydrofuran: In a 100 mL round-bottomed flask, under N_2 equipped with a stirring bar, 1.8 g of benzoyl acetate (1.0 eq.), and 1.46 g of styrene (1.0 eq.) are placed. Potassium acetate (0.74 g, 1.0 eq.) dissolved in 37 mL of acetic acid is added to the flask. Manganese acetate (4.4 g, 2.2 eq.) is then added. The reaction

mixture is then heated in a 75 ^{o}C oil bath and is allowed to stir until the cloudy brown color changes to clear yellow. The mixture is allowed to cool to room temperature with stirring under N_2. The reaction is then quenched with H_2O (35 mL), and extracted with $CHCl_3$ (4 X 30 mL). The extracts are combined and washed with H_2O (6 X 30 mL) and dried over anhydrous $MgSO_4$. The solvent is removed, and the oil is purified by MPLC eluting with 20% EA/PE.

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