ABSTRACT

A B S T R A C T

CHAPTER I - SYNTHESIS OF 1-TRIACONTANOL

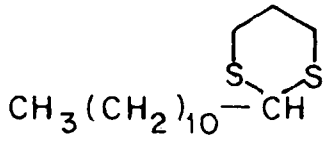
1-Triacontanol (1), a naturally occurring plant product possesses plant growth regulating properties. In this chapter two convenient syntheses of 1-triacontanol were discussed.

$$CH_3(CH_2)_{29}OH$$

1

1. The Dithiane approach

The strategy involved in this approach was the synthesis of 2-dodecyl-1,3-dithiane (2), and a C_{18} bromo compound (3); their condensation and further elaboration to 1.



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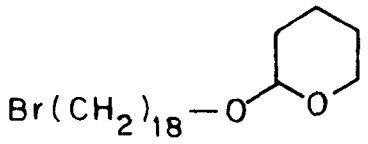

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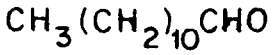

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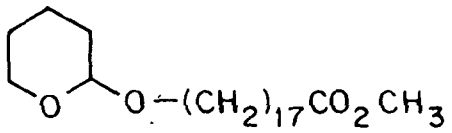
The synthon 2 was prepared starting from 1-dodecanol which on oxidation with pyridiniumdichromate gave the aldehyde 4. Compound 4 was further treated with 1,3-propane dithiol to afford 2. Other synthon, bromide 3 was prepared starting from naturally occurring 18-hydroxy-octadecanoic acid. It was esterified with diazomethane

and hydroxyl group was protected with dihydropyran to afford compound 5. Compound 5 was reduced with lithium aluminiumhydride to give the alcohol 6, which was then converted to the bromide 3 via the corresponding mesylate 7.



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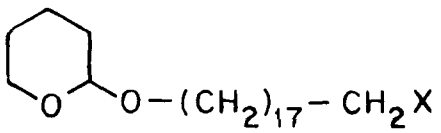


6 X = OH
7 X = OSO_2CH_3

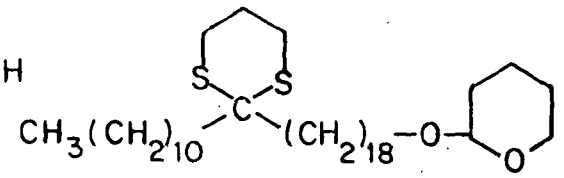
Alternatively, bromide 3 was prepared by a shorter route, in which 18-hydroxyoctadecanoic acid on treatment with 48% HBr furnished bromoacid 8, which on reduction with diborane gave 18-bromooctadecanol (9). Compound 9 was treated with dihydropyran to give the bromide 3.

$Br(CH_2)_{17}COOH$

8

$Br(CH_2)_{17}CH_2OH$

9



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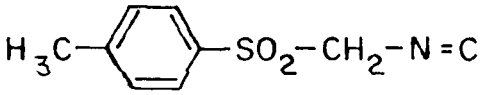
Metallation of the dithiane 2 with n-BuLi, followed by an alkylation with the bromide 3 afforded the desired alkylated product 10, which on Raney nickel reduction followed by THP deprotection gave 1-triacontanol.

2. The TosMIC approach

Since the above synthesis did not provide 1 in large quantities, in order to prepare it in substantial amounts, an alternative route was developed by making use

of tosylmethylisocyanide (TosMIC).

The salient features of this synthesis were the successive alkylations of TosMIC (11), using appropriate alkyl halides (12 and 13) and subsequently converting to 1-triacontanol.



11

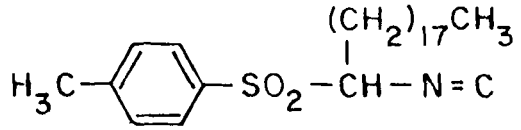
$CH_3(CH_2)_{17}I$

12

$Br(CH_2)_{10}CO_2CH_3$

13

The first alkylation of 11 with 1-iodooctadecane (12) was achieved under phase transfer catalyst conditions using tetrabutyl ammoniumhydroxide as catalyst, to furnish the monoalkylated product 14. Compound 14 on subsequent alkylation with bromide 13 in presence of sodium hydride, followed by hydrolysis with conc. hydrochloric acid afforded methyl 12-oxotriacontanoate (15). Compound 15 was treated with 1,3-propane dithiol and the resulting thioketal 16 was reduced with Raney nickel to give methyltriacontanoate (17), which on reduction with lithium aluminiumhydride gave 1-triacontanol.



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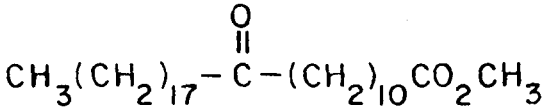

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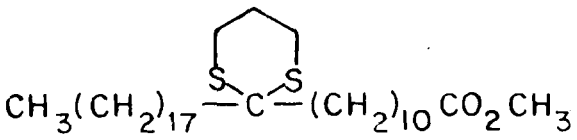

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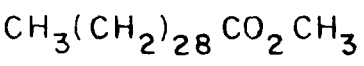

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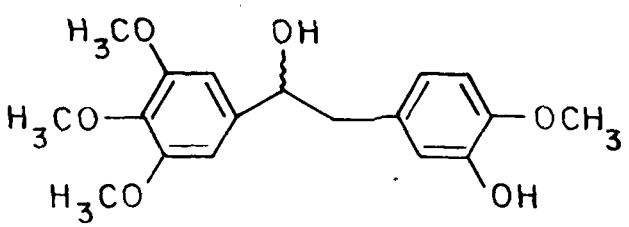
All these reactions in this sequence gave excellent yields whereby providing a method for the synthesis of 1-triacontanol in large quantities..

CHAPTER II - SYNTHESIS OF (±)COMBRETASTATIN

(±) Combretastatin (18) is a plant product isolated by Pettit et al. from the South African tree Combretum caffrum and was found to possess anti-neoplastic activity. Its limited availability from natural sources prompted to develop a synthetic route to (±)18, which can provide sufficient material for pharmacological further evaluation of its/properties.



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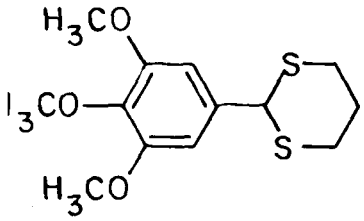
Main strategy in the present synthesis of (±)18 involved the C-C bond formation, through the 'Umpolung' activity of the dithiane derivative 19 with a suitably substituted halide 20 and further elaboration leading to (±)18.



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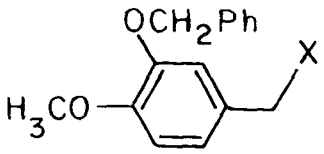


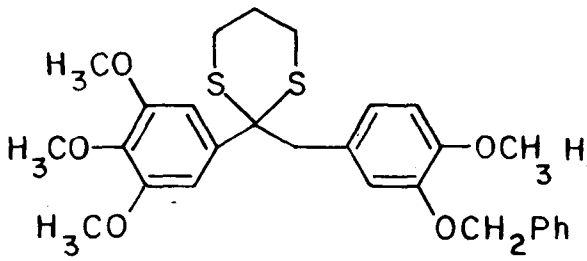
20 X = Br

21 X = OH

2-(3,4,5-trimethoxyphenyl)-1,3-dithiane (19) was prepared by the treatment of 3,4,5-trimethoxybenzaldehyde with 1,3-propanedithiol. Other synthon 3-benzyloxy-4-methoxybenzylbromide (20) was prepared starting from isovanillin. Thus isovanillin was O-benzylated, and the resulted product was reduced with sodiumborohydride to afford alcohol 21 which on treatment with phosphorustribromide gave the bromide 20.

Metallation of 19 with n-BuLi, followed by alkylation with the bromide 20 gave the alkylated product 22, which on dethioketalisation with mercuric chloride furnished the ketone 23. Compound 23 was debenzylated with trifluoroacetic acid and the resulted product 24

was reduced with sodiumborohydride to afford (±)combretastatin (18).



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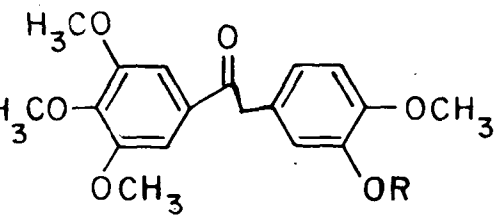
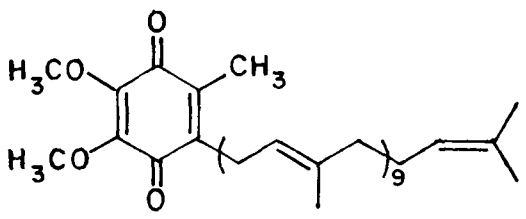


23 R = CH_2Ph

24 R = H

CHAPTER III - SYNTHESIS OF UBIQUINONE-10

Ubiquinones are a family of 2,3-dimethoxy-5-methyl-6-polyprenyl-1,4-benzoquinones. Ubiquinone-10 (25) is known to be involved in respiratory and photosynthetic electron transport systems and exhibits clinical activity. In this chapter the synthesis of ubiquinone-10 (25) was discussed.



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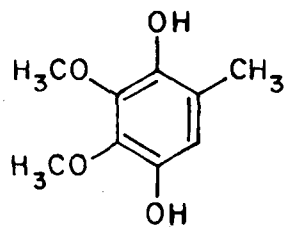

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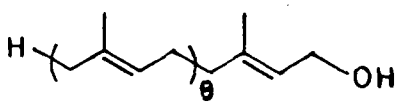
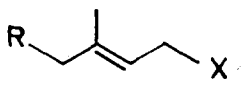


27

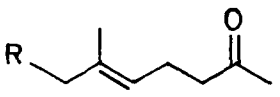
The present synthetic strategy for the synthesis of 25 involved the condensation of 2,3-dimethoxy-5-methyl-1,4-hydroquinone (26), with a C_{50} alcohol 27 followed by oxidation.

The C_{50} alcohol 27 was prepared starting from naturally occurring solanesol (28), an all trans C_{45} alcohol, which was isolated from tobacco waste. Solanesol (28) was treated with phosphorus tribromide to give the corresponding bromide 29, which on treatment with ethylacetoacetate in presence of sodium ethoxide gave a product which on decarboethoxylation afforded solanesyl acetone 30. Wittig condensation of 30 with triethylphosphonoacetate gave the ester 31, which on reduction with lithium monoethoxyaluminiumhydride afforded the C_{50} alcohol 27.



28 X = OH

29 X = Br



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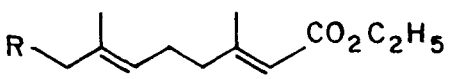

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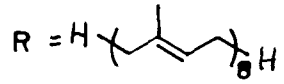
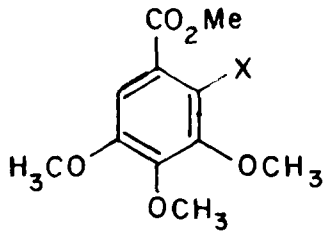


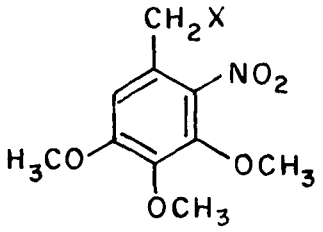
Aromatic moiety 26 was synthesised starting from methyl-3,4,5-trimethoxybenzoate 32. Compound 32 was treated with conc. nitric acid in acetic anhydride to give the nitro compound 33, which was subjected to lithium

aluminiumhydride reduction to furnish the alcohol 34.



32 X = H

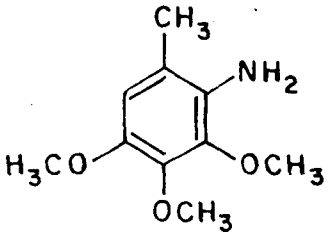
33 X = NO_2



34 X = OH

35 X = Br

36 X = H



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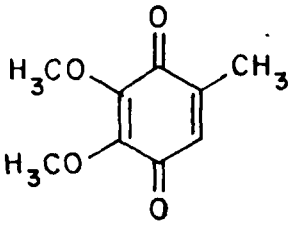


38

Alcohol 34 on treatment with phosphorustribromide gave the bromide 35, which was transformed into 2-nitro-3,4,5-trimethoxytoluene (36) on treatment with triphenylphosphine, followed by reaction with 10% methanolic sodium hydroxide. Compound 36 was subjected to hydrogenation with Pd-C in ethanol to give 37, which was oxidised with potassium-dichromate in sulfuric acid to afford 2,3-dimethoxy-5-methyl-1,4-benzoquinone (38). Reduction of quinone 38 with sodiumdithionate afforded the hydroquinone 26.

The condensation of 26 with 27 was effected in

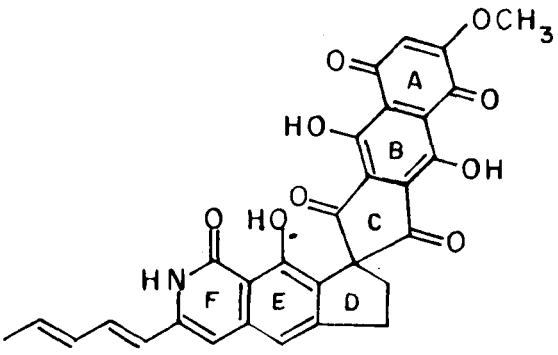
presence of borantrifluoride-etherate in dioxane to afford the corresponding hydroquinone which was oxidised with ferric chloride to furnish ubiquinone-10 (25).

CHAPTER IV - SYNTHETIC APPROACHES TOWARDS FREDERICAMYCIN-A

Fredericamycin-A (39), a novel antibiotic from Streptomyces griseus exhibits antibacterial, antifungal cytotoxic and antitumour activity and possesses an entirely novel spiro[4,4]nonane system.

Recently in these laboratories, the synthesis of model spiro [4,4]nonane system (40) has been accomplished starting from 41 and 42 employing Dieckmann condensation to afford 43, which was subsequently converted to 40.

Having established the methodology for spiro[4,4] nonane system, and based on the above strategy fredericamycin (39) could be prepared from two synthons 44 and 45.



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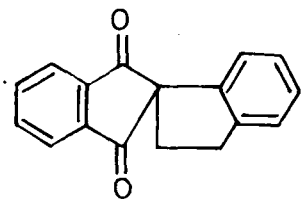

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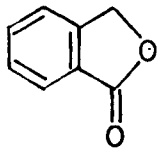

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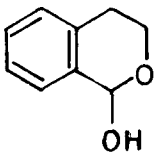

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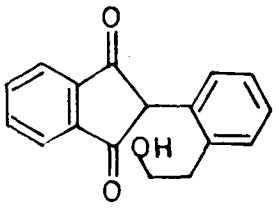

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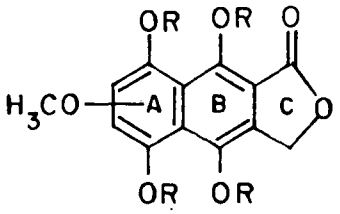

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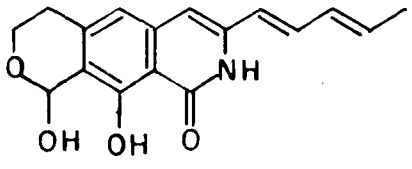

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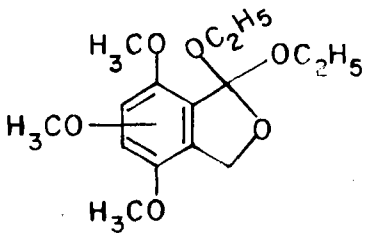
In this chapter the synthesis of the ABC synthon 44 was dealt with. The strategy involved in the present synthesis was to build the complete ABC skeleton by a Diels-Alder reaction between the orthoester 46 and dimethylacetylene dicarboxylate and further elaboration to 44.



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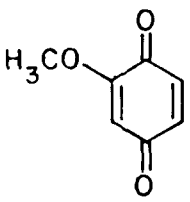

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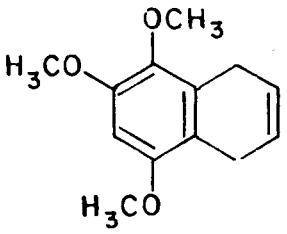

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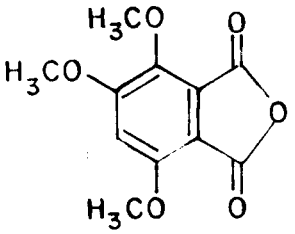

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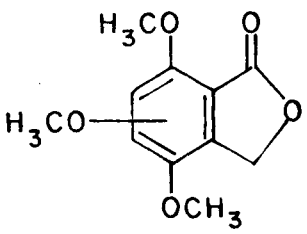

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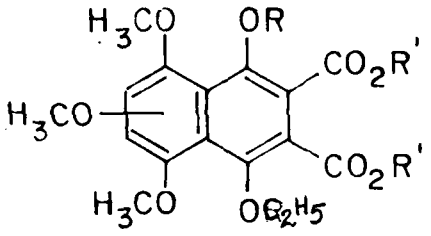
The orthoester 46 was prepared starting from vanillin, which on oxidation with alkaline hydrogen-peroxide, followed by potassiumdichromate treatment afforded quinone 47. Compound 47 on Diels-Alder reaction with 1,3-butadiene followed by O-methylation with dimethylsulfate furnished the adduct 48. Oxidation of 48 with potassium permanganate and treatment of the resulted diacid with aceticanhydride gave anhydride 49. Anhydride 49 on reduction with sodiumborohydride furnished the phthalide 50.

Phthalide 50 was converted to the corresponding orthoester 46 by sequential treatment with Meerwein's salt, followed by sodium ethoxide. Diels-Alder reaction of 46 with dimethyl acetylenedicarboxylate in presence of catalytic amount of acetic acid gave the hydroxy diester 51 which was O-ethylated with ethyl iodide in

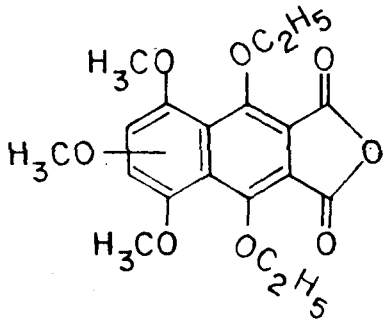
presence of sodiumhydride to furnish diethoxy diester 52.



51 R = H , R' = CH_3

52 R = C_2H_5 , R' = CH_3

53 R = C_2H_5 , R' = H



54

Compound 52 on treatment with methanolic sodium hydroxide gave the diacid 53 which on reaction with acetic anhydride gave the corresponding anhydride 54. Compound 54 was reduced with sodiumborohydride to give isomeric mixture of 44. Thus 44 constitutes the ABC synthon desired for achieving the total synthesis of fredericamycin-A.