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PROCESSES FOR PRODUCING DOXORUBICIN, DAUNOMYCINONE, AND DERIVATIVES OF DOXORUBICIN

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[54] **PROCESSES FOR PRODUCING DOXORUBICIN, DAUNOMYCINONE, AND DERIVATIVES OF DOXORUBICIN**

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[58] **Field of Search** 552/201, 202; 536/6.4; 549/363

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,697,005 9/1987 Swenton et al. 552/201

OTHER PUBLICATIONS

Swenton et al., II Jol. Amer. Chem. Soc., vol. 100(19), Sep. 1978, pp. 6188-6195, "A Regiospecific Synthesis of the Anthracyclic Aglycones, Daunomycinone and Adriamycinone".

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[57] **ABSTRACT**

To produce doxorubicin and its analogues methyl 3alpha, 5alpha-dihydroxy-5beta-(trimethylsilylethynyl)-2alpha-nitromethylcyclohexane-1beta-carboxylate acetonide is condensed with 1,4-dihydro-4,4,5-trimethoxy-1-oxonaphthalene in the presence of 1,8-diazabicyclo-[5.4.0]undec-7-ene in an aprotic solvent to produce 3-[(2beta-carbomethoxy-4beta-ethynyl-4alpha, 6alpha-(di-O-isopropylidenyl)cyclohexanyl-1-yl]-nitromethyl-4,4,5-trimethoxy-1-oxo-1,2,3,4-tetrahydronaphthalene; which is cyclized to produce 9beta-ethynyl-12-hydroxy-7alpha,9alpha-(di-O-isopropylidenyl)-6-nitro-4,5,5-trimethoxy-5,5a,6-,6a,7,8,9,10,10a,11-decahydro -11-naphthacenone. The decahydro-11-naphthacenone is converted to 7alpha-9alpha,(di-O-isopropyl-idenyl)-4,5-dimethoxy-9beta-ethynyl-12-hydroxy-6-nitro-6,6a,7,8,9,10,10a,11-octahydro-11, -naphthacenone. The octahydro-11-naphthacenone is oxidized to 7alpha-9alpha, (di-O-isopropyl-idenyl)-9beta-ethynyl-11-hydroxy-4-methoxy-6-nitro-7,8,9,10,-tetrahydro-5,12-naphthacenedione which is converted to 6-desoxy-6-nitrodaunomycinone, daunomycinone and related 6-substituted analogues of daunomycinone.

37 Claims, No Drawings

PROCESSES FOR PRODUCING DOXORUBICIN, DAUNOMYCINONE, AND DERIVATIVES OF DOXORUBICIN

BACKGROUND OF THE INVENTION

This invention relates to a process for producing doxorubicin (adriamycin), and derivatives of doxorubicin, through a novel synthesis of daunomycinone and its derivatives. These mycinones can be coupled by known methods to daunosamine to produce doxorubicin and its corresponding derivatives.

It is known that doxorubicin is isolated from *Streptomyces peucetius.* A suitable process for this isolation is described by F. Arcamone, in "Duxorubicin Anticancer Antibiotics," (Academic Press, New York (1981). Moreover, synthetic routes to doxorubicin are known and these are summarized, for example, by F. Arcamone (loc. cit.), K. Krohn, *Angew. Chem. Int. Ed. Engl.,* volume 25 (1986), page 790 and *Tetrahedron,* volume 46 (1989), page 291 and T. R. Kelly, *Tetrahedron Symposium-in-Print,* volume 40 (1984), pages 4537–4793.

A representative prior art procedure for converting daunomycinone to adriamycin is that proposed by Arcamone et al., U.S. Pat. No. 3,803,124. The prior art methods of obtaining daunomycinone have the disadvantage of being expensive.

SUMMARY OF THE INVENTION

It is an object of the invention to provide a novel synthesis of doxorubicin.

It is a still further object of the invention to provide a novel process for synthesis of derivatives of doxorubicin.

It is a still further object of the invention to provide a novel process for the synthesis of doxorubicin and its derivatives in which the A ring is made stereo selectively with its functionality already established and then joined to the CD portion, with the relationship between the C-7 and C-9 hydroxyls established stereoselectively before the tetracyclic skeleton is constructed.

It is a still further object of the invention to provide a novel process for the synthesis of daunomycinone that proceeds in DCAB order with the B ring formed last.

It is a still further object of the invention to provide a novel process of producing intermediates for the synthesis of daunomycinone, namely, methyl 3alpha,5alpha-dihydroxy-5beta-(trimethylsilylethynyl)-2alpha-nitromethylcyclohexane-1-beta-carboxylate and the 3,5-acetonide of methyl 3alpha,5alpha-dihydroxy-5beta-(tri-methylsilylethynyl)-2alpha-nitromethylcyclohexane-1-betacarboxylate.

It is a still further object of the invention to provide novel synthetic routes to daunomycinone and derivatives of this compound.

In accordance with the invention a novel synthesis of daunomycinone is provided in which the A-ring precursor of the compound is synthesized from m-anisic acid. The A-ring precursor, methyl cis-2,3-epoxy-5-hydroxy-5-(trimethylsilylethynyl)cyclohexane-1-carboxylate, is converted to methyl cis-3,5-dihydroxy-5-(trimethylsilylethynyl)cyclohex-1-ene-1-carboxylate which is nitromethylated to produce the required 2alpha-nitromethyl compound. The 3,5-acetonide of the 2alpha-nitromethyl compound is coupled with a juglone alkyl ether ketal and cyclized to a tetracyclic intermediate. The latter can be converted to daunomycinone and many of its derivatives.

More specifically, this process for the production of daunomycinone, comprises the steps of: (1) condensing methyl 3alpha,5alpha-dihydroxy-5beta-(trimethylsilylethynyl)-2alphanitromethylcyclohexane-1-beta-carboxylate acetonide with 1,4-dihydro-4,4,5-trimethoxy-1-oxonaphthalene in the presence of 1,8-diazabicyclo[5.4.0]-undec-7-ene in an aprotic solvent to produce a 3-[(2beta-carbomethoxy-4beta-ethynyl-4alpha,6alpha-(di-O-isopropylidene)cyclohexanyl-1-yl]-nitromethyl-4,4; 5-trimethoxy-1-oxo-1,2,3,4-tetrahydronaphthalene; (2) cyclizing the thus-produced 1-oxotetrahydronaphthalene to produce 7alpha, 9alpha-(di-O-isopropylindenyl)-4-6-nitro-4,5,5-trimethoxy-5,5a,6,6a,7,8,9,10,-10a, 11-dechydro-11-naphthacenone; (3) converting the decahydro-11-naphthacenone to 4,5-dimethoxy-7alpha,9alpha-(di-O-isopropylidenyl)-9beta-ethynyl-12-hydroxy-6-nitro-6,6a,7,8,9,10,10a-octahydro-11-naphthacenone; (4) oxidizing the thus produced octahydro-11-naphthacenone to 7alpha-9alpha-(di-O-isolpropylidenyl)-9beta-ethynyl-11-hydroxy-4-methoxy-6-nitro-7,8,9,10-tetrahydro-5-12-naphthacenedione; (5) hydrolysing the tetrahydro-5,12-naphthacenedione to 6-desoxy-6-nitro-daunomycinone; (6) reducing the nitro compound to 6-desoxy-6-aminodaunomycinone; (7) diazotising the amino compound and obtaining from it, daunomycinone, the 6-desoxy-6 halo and cyanodaunomycinones and compounds derived from them.

To produce the methyl 3alpha,5alpha-dihydroxy-2alpha-nitromethyl-5beta-(trimethylsilylethynyl)cyclohexane-1beta carboxylate, methyl cis-3,5-dihydroxy-5-(trimethylsilylethynyl)-cyclohex-1-ene-1-carboxylate is reacted with nitromethane in the presence of 1,8-diazabicyclo [5.4.0]undec-7-ene or sodium hydride in an aprotic solvent that can act as a hydrogen bond acceptor.

To synthesize methyl cis-3,5-dihydroxy-5-(trimethylsilylethynyl)cyclohex-1-ene-1-carboxylate, m-anisic acid is subject to the Birch reduction with lithium in ammonia to produce 5-oxocyclohex-2-ene-1-carboxylic acid, followed by methylation of thusproduced cyclohex-2-ene-1-carboxylic acid to methyl 5-oxocyclohex-2-ene-1-carboxylate with diazomethane, trimethylsilyl-ethynylation of thus-produced cyclohex-2-ene-1-carboxylate with cerium dichloride trimethylsilylacetylene to produce methyl cis-5-hydroxy-5-(trimethylsilylethynyl)cyclohex-2-ene-1-carboxylate, conversion to an epoxide and opening of the resulting epoxide ring to produce the cis-3,5-dihydroxy compound.

In this process for synthesizing daunomycinone there are several especially significant procedural steps, such as: (1) the reaction mixture is kept between −20 to 20 degrees centigrade during esterification with diazomethane; (2) any ethanol and water present in the esterification reaction mixture is removed by azeotropic distillation with benezene to produce methyl ester; (3) methyl ester is immediately treated with cerium dichloride trimethylsilylacetylene at a low temperature, such as −50 to −78 degrees centigrade, to prevent formation of a lactone; (4) the epoxide is formed by oxidation with tert.-butylhydroperoxide in the presence of molybdenum hexacarbonyl catalyst and the epoxide that is produced is isolated; and (5) the thus-formed epoxide ring is opened with 1,8-diazabicyclo[5.4.0]-undec-7-ene. The cerium reagent must be added to the keto ester to avoid a migration of the double bond.

A feature of the synthesis is the production of the 4,4-dimethylacetal of 5-alkoxy-1,4-naphthoquinones oxidation of 5-alkoxy-1-naphthol with iodobenzene diacetate in methanol. The 5-alkoxy-1-naphthol, in which the alkoxy is of 1-6 carbon atoms as described in Moore, H. W.; Lee, S.; Rutolo, D.; Sheldon, R., *J. Org. Chem.*, 1978, 43, 2304–2306. Generally, this process may include the steps of: (1) alkylating 1,5-dihydroxynaphthalene with an excess of alkyl iodide in the presence of a base, e.g. potassium carbonate in an aprotic solvent to produce 1,5-dialkoxynaphthalene; (2) dealkylating the thus-produced 1,5-dialkoxynaphthalene with an alkali metal alkanethiolate to remove selectively one alkyl moiety; and (3) acidifying the alkoxide that is produced to form 5-alkoxy-1-naphthol.

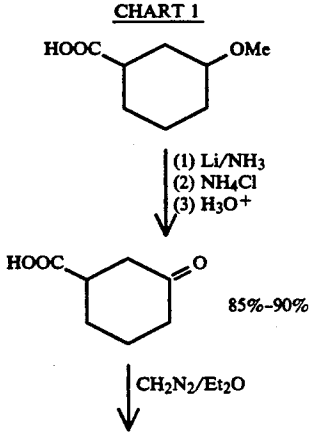
As can be understood from the above description, the processes of this invention permit the manufacture of doxorubicin less expensively and permit the effective preparation of derivatives thereof.

DETAILED DESCRIPTION

The synthesis of the intermediate, required for elaboration of the A-ring, 3alpha,5alpha-dihydroxy-2alpha-nitromethyl-5beta-(trimethylsilylethynyl)cyclohexane-1beta-carboxylate acetonide is shown in charts 1 and 2. It has been found that a 58 percent overall yield of methyl cis-3,5-dihydroxy-5-(trimethylsilylethynyl)cyclohex-1-ene-1-carboxylate can be obtained by keeping the reaction mixture cold during esterification with diazomethane and removing any ethanol and water present in the esterification reaction mixture by azeotropic distillation with benzene; quickly reacting to the thus-produced methyl ester with added cerium dichloride trimethylsilyl-acetylene at a low temperature to prevent formation of a lactone; forming the epoxide by oxidation with tert.-butyl hydroperoxide in a fluxing benzene solution in the presence of molybdenum hexacarbonyl catalyst and isolating the thus-produced epoxide and opening the thus-formed epoxide ring with 1,8-diazabicyclo-[5.4.0]-undec-7-ene. Without the recited precautions and using completely anhydrous cerium dichloride, the yield from m-anisic acid is less than 10 percent.

Methyl 3alpha,5alpha-dihydroxy-2alpha-nitromethyl-5beta-(trimethylsilylethynyl)-cyclohexane-1beta-carboxylate was obtained from methyl cis-

CHART 1



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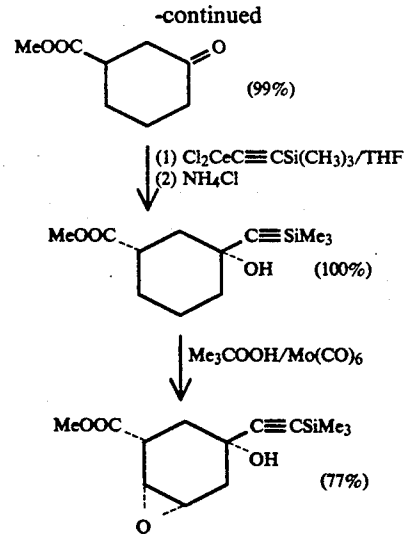
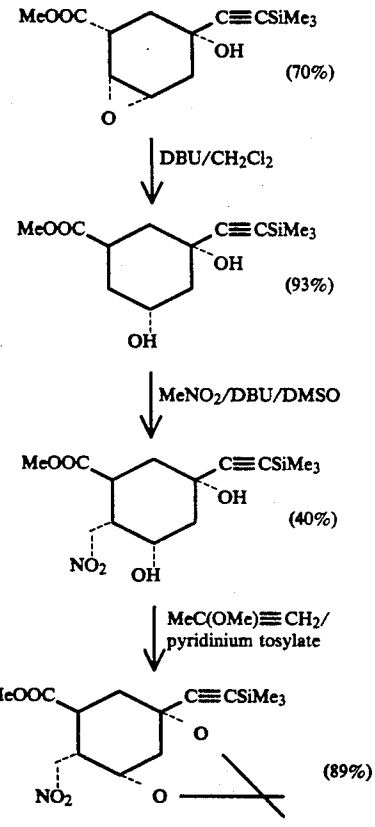


CHART 2



2,3-epoxy-5-hydroxy-5-(trimethylsilylethynyl) cyclohexane-1-carboxylate by reaction with nitromethane in the presence of 1,8-diazabicyclo[5.4.0-undec-7-ene in an aprotic solvent that can serve as a hydrogen bond acceptor. Alternatively, methyl 3alpha,5alpha-dihydroxy-2alpha-nitromethyl-5beta-(trimethylsilylethynyl) cyclohexane-1betacarboxylate was obtained from methyl cis-3,5-dihydroxy-5-(trimethylsilylethynyl)cyclohex-1-ene-1-carboxylate-and nitromethane in the presence of 1,8-diazabicyclo-[5.4.0]-undec-7-ene or sodium hydride in an aprotic solvent.

The aprotic solvent used for the nitromethylation reaction may be selected from the following: hexame-

thylphosphoramide, dimethyl sulfoxide and NN'-dimethyl-NN'-propylene urea. The preferred aprotic solvent is dimethyl sulfoxide. Nitromethane also adds to the 3,5-di-(terbutyldimethylsilyl) ether of the diol.

The nitromethylation is conveniently carried out at ambient temperature for a time necessary to complete the reaction. The required time is of the order of 12 to 24 hours. If the reaction becomes exothermic, cooling to 15 to 25 degrees centigrade is preferred.

An acetonide is formed from 3alpha,5alpha-dihydroxy-5beta-(trimethylsilylethynyl)-2alpha-nitromethylcyclohexane-1beta-carboxylate by treatment with an acetonide-forming reagent. Representative acetonide-forming agents include, but are not limited to, 2-methoxypropene. Preferably, the acetonide-forming reagent is 2-methoxypropene.

The acetonide-forming reaction is carried out in the presence of a catalyst, such as pyridinium tosylate or n-toluenesulfonic acid. A preferred catalyst is pyridinium tosylate.

An inert solvent is used for the reaction. Benzene, heptane, toluene are representative of solvents suitable for the reaction. When benzene is used as the solvent, the reaction goes to completion within a few minutes' heating under reflux. Conditions appropriate for other solvents can be determined by routine experimentation.

The synthesis of a representative 1,4-dihydro-4,4,5-trimethoxy-1-oxo-naphthalene is shown in Chart 3. The initial steps of the synthesis include alkylation of both hydroxyl groups of 1,5-dihydroxynaphthalene, followed by selective removal

CHART 3

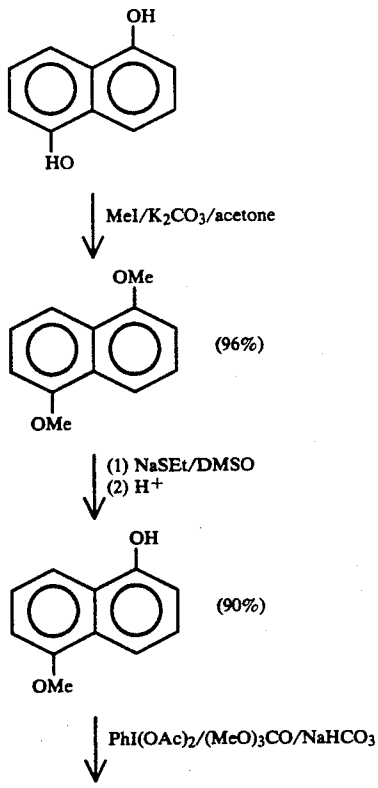


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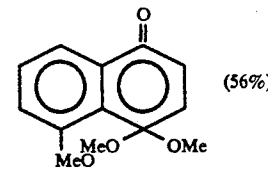
CHART 3



of only one alkyl to give 5-alkoxy-1-naphthol. The alkyl moiety can be selected from primary alkyls of 1-6 carbon atoms, such as methyl, ethyl and n-propyl. The alkyl iodide is used in an amount in excess of that, required to alkylate both hydroxyl groups. Preferably, a molar ratio in the range of 4:1 to 2.5:1 of alkyl iodide to 1,5-dihydroxynaphthalene, is used. Most preferably, the ratio is about 3.5:1.

The etherification reaction is conducted in the presence of a base, which is normally selected from organic and inorganic bases. Representative bases include, but are not limited to, sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, pyridine, triethylamine. A preferred base is potassium carbonate. The amount of base employed should be in the range of 3.5 moles to 4.5 moles, per mole of 1,5-dihydroxynaphthalene.

The aprotic solvent can be selected from acetone, methylethyl ketone, methylisobutyl ketone, tetrahydrofuran, acetonitrile, dimethyl sulfoxide. Preferably, the solvent is acetone.

The alkali metal alkanethiolate, used for removing one alkyl group from the intermediate dialkoxy compound can be selected from sodium and potassium alkanethiolates, having 1–6 carbon atoms in the alkane moiety. Preferably, the alkali metal alkanethiolate is sodium methanethiolate or ethanethiolate. The resulting alkali metal alkoxide can be acidified with any mineral acid, of which sulfuric acid, hydrochloric acid and phosphoric acid are representative.

The 5-alkoxy-1-napthol produced in this way can be converted, for example, to a corresponding juglone alkyl ether 4-ethylene ketal by reaction with ethylene glycol and thallium trinitrate or lodobenzediacetate in trimethyl orthoformate. A preferred ketal for downstream synthesis is 1,4-dihydro-4,4-ethylenedioxy-5-methoxy-1-oxonaphthalene, produced from 5-methoxy-1-naphthol and ethylene glycol under the conditions stated.

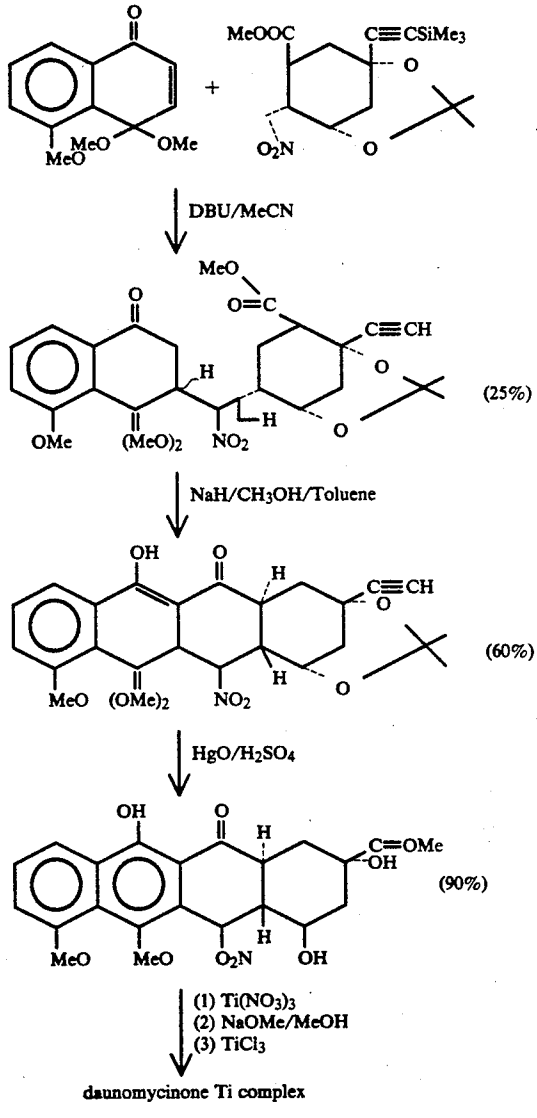
A most preferred product for downstream synthesis is 1,4-dihydro-4,4,5-trimethoxy-1-oxonaphthalene. This is preferably produced from 5-methoxy-1-naphthol by reaction with methanol and iodobenzene diacetate in trimethyl orthoformate. It will be understood that alkanols of 2–3 carbon atoms can be used to produce higher ketals by a similar process.

The synthesis of daunomycinone from methyl 3alpha,5alpha-dihydroxy-2alpha-nitromethyl-5beta(trimethylsilylethynyl)cyclohexane-1beta carboxylate acetonide and a representative 1,4-dihydro-4,4-5-trimethoxy-1-oxonaphthalene is shown in Chart 4. Condensation to the 1-oxotetrahydronaphthalene is carried out in an aprotic solvent. The aprotic solvent may be selected from dimethyl sulfoxide, hexamethylphosphoramide and acetonitrile. Acetonitrile is preferred. The reaction is carried out at ambient temperature. Conversion to a representative intermediate, 3-[(2beta-carbomethoxybeta-ethynyl-4alpha,6alpha-(di-O-isopropylidenyl)-

cyclohexanyl-1-yl]-nitromethyl-4,4,5-trimethoxy-1-oxo-1,2,3,4-tetrahydronaphthalene is complete within 4–6 days.

The thus-produced 1-oxotetrahydronaphthalene is preferably cyclized with an alkali metal alkoxide of 1–6 carbon atoms. Suitable alkoxides can be prepared from alkanols of 1–6 carbon atoms, as above, and an alkali metal hydride. Alkali metal hydrides include sodium hydride or potassium hydride, of which sodium hydride is preferred. Most preferably, the alkali metal alkoxide is sodium

CHART 4



methoxide. The cyclization is carried out in an inert solvent, such as benzene, hexane or toluene.

A representative cyclic product of this condensation is 7alpha,9alpha-(di-O-isopropylidenyl)-9beta-ethynyl-6-nitro-4,-5-trimethoxy-5,5a, 6,6a,7,8,9,10,10a,11-decahydro-11-naphthacenone.

The thus produced decahydro-11-naphthacenone loses methanol in the presence of an acidic catalyst to yield 7alpha,9alpha-(di-O-isopropylidenyl)-4,5-dimethoxy-9beta-ethynyl-12-hydroxy-6-nitro-6,6a,7,8,9,10,10a,11-octahydro-11-naphthacenone. Possible catalysts include sulfonic acids e.g. methanesulfonic acid; pyridinium p-toluenesulfonate is preferred. A variety of aprotic solvents e.g. aromatic hydrocarbons, tetrahydrofuran, methylene chloride may be used; methylene chloride is preferred.

The thus produced octahydro-11-naphthacenone was then oxidized to 7alpha,9alpha- (di-O-isopropylidenyl)-9beta-ethynyl-11-hydroxy-4-methoxy-7,8,9,10-tetrahydro-5,12-naphthacenedione. Oxidizing agents include cerium ammonium nitrate (CAN) and thallium trinitrate (TTN); solvents include methanol, acetone and acetonitrile. The preferred conditions are CAN in acetone with dichlorodicyanobenzoquinone (DDQ) added in catalytic amount. The thus produced 5,-12-naphthacenedione is then hydrolysed with acid in the presence of mercuric oxide to give 6-dexosy-6-nitrodauomycinone.

The 6-nitro compound can then be reduced to 6-desoxy-6-aminodaunomycinone from which daunomycinone and a variety of mycinones can be produced. These mycinones can be coupled by known methods to daunosamine to produce doxorubicin and its corresponding derivatives.

In one embodiment, the aprotic solvent for condensing the acetonide with 1,4-dihydro-4,4,5-trimethoxy-1-oxonaphthalene is acetonitrile; the thus-produced 1-oxotetrahydronaphthalene is cyclized with sodium methoxide; the thus-produced decahydro-11-naphthacenone is converted to the octahydro-11-naphthacenone in an acidic medium; the thus-produced octahydro-11-naphthacenone is oxidized to the tetrahydro-5,12-naphthacenedione with the thusproduced tetrahydro-5,12-naphthacenedione being converted to 6-desoxy-6-nitrodaunomycinone by hydrolysis and from this compound into daunomycinone and 6 to 8 daunomycinones in which the substituent at C_6 has been changed.

In a further embodiment, the aprotic solvent for condensing the acetonide with 1,4-dihydro-4,4,5-trimethoxy-1-oxonaphthalene is acetonitrile; the thus-produced 1-oxotetrahydronaphthalene is cyclized with sodium methoxide; the thus-produced decahydro-11-naphthacenone is converted to 9beta-acetyl-4,5-dimethoxy-6-nitro-7alpha,9alpha,12-trihydroxy-6,6a,7,8,9,10,10a,11-octahydro-11-napthacenone by hydrolysis with acid in the presence of mercuric oxide in an acidic medium; the thus-produced 9-beta-acetylocatahydro-11-naphthacenone is oxidized to 7alpha,9-alpha-dihydroxy-4-methoxy-6-nitro-6,6a,7,8,9,10,10a,11-octahydro-5,11,12-naphthacenetrione with thallium nitrate and the produced octahydro-5,11,12-naphthacenetrione is converted to daunomycinone.

In a preferred embodiment, 6-desoxy-6-nitrodaunomycinone was converted into 6-desoxy-6-aminodaunamycinone by reduction with $SnCl_2H_2O$ in methanol in the presence of sodium on acetate at room temperature and the lenco product reoxidized with cerium ammonium nitrate.

The amino daunomycinone has been converted into its diazonium compound with its amyl nitrite in dimethoxyethane and then acid and finally mercuric oxide was added to form daunomycinone. A variety of other 6-desoxy-6-substituted daunomycinones are available from the diazonium compound.

EXAMPLES

Without further elaboration it is believed that one skilled in the art can, using the preceding description,

utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative and not limitative of the remainder of the disclosure in any way whatsoever.

In the following examples, the temperatures are set forth uncorrected in degrees centigrade. Unless otherwise indicated, all parts and percentages are by weight.

Materials and Methods

^1H NMR spectra were recorded on a Varian EM-390 (90 MHx), a Varian VXR-200 (200MHx) or a Nicolet 1180 WB (360 MHz) spectrometer. Data are reported as chemical shifts in parts per million referenced to trimethylsilane internal standard (0 ppm) or to the residual chloroform peak of deuteriochloroform (7.26 ppm). Multiplicity, number of protons and coupling constants are reported. Couplings and/or coupling constants were determined using the COSY technique or by proton irradiation experiments.

^{13}C NMR spectra were obtained on a Varian VXR200 (50.4 MHz) spectrometer. Chemical shifts are referenced to the center peak of the residual chloroform triplet (77.0 ppm).

Ultraviolet spectra were obtained on a Hewlett-Packard 8450 UV-Vis spectrophotometer.

Infrared absorption spectra were recorded on a Perkin-Elmer Model 283 or an Analect RFX-30 spectrophotometer and are referenced to polystyrene (1601 cm^{-1}).

Elemental analyses were carried out by Desert Analytics (Tuscon, Ariz.).

Mass spectra were provided by the Midwest Center for Mass Spectrometry, University of Nebraska-Lincoln.

Melting points were determined in open-end capillary tubes on a Mel-Temp apparatus.

Column chromatography was carried out on E. Merck silica gel 60 (Flash, 40-230 mesh) and all thin layer chromatography (TLC) was carried out on commercial silica gel plates (Analtech Silica HLF 250 m or Merck Silica gel 60F 254).

High performance liquid chromatography (HPLC) was performed on a Waters Associates Model 600E chromatography apparatus, equipped with a Waters Associates Model R403 Differential Refractometer, using normal-phase silica gel columns.

Solvents were distilled before use over an appropriate drying agent under a nitrogen atmosphere. All reactions requiring anhydrous conditions were done under nitrogen in flame-dryed flasks. Solvents were evaporated using a Buchi rotary evaporator, then by evacuation at about 0.10 mm Hg at room temperature.

EXAMPLE 1

5-Oxocyclohex-2-ene-1-carboxylic Acid

The procedure of Biffin et al., *Aust. J. Chem.*, vol. 25 (1972), page 1329, was used.

To a stirred slurry of 30 g (0.21 mol) of m-anisic acid (3-methoxybenzoic acid) in 300 mL of liquid ammonia were slowly added small pieces of lithium (3.5 g, 0.5 mol). Additional lithium (0.5 g, 0.07 mol) was added to maintain the blue color of the solution. The mixture was stirred for 2 hours and then cautiously quenched with solid ammonium chloride (45 g, 0.84 mol).

Ammonia was allowed to evaporate at room temperature. The last traces of ammonia were removed by warming the mixture under aspirator pressure. The resulting residue was dissolved in 200 mL of ice water and acidified to pH 1 with conc HCl. The resulting solution was extracted with four 100-mL portions of ethyl acetate. The combined ethyl acetate extracts were washed with one 50-mL portion of saturated sodium chloride solution, dried over sodium sulfate and evaporated to dryness. Crude semi-crystalline acid (24.1 g) was washed with a small amount of cold ether to yield 5-oxocyclohex-2-ene-1-carboxylic acid, off-white crystals, mp 98–101 degrees centigrade, lit (Biffin et al., supra, 98 to 99 degrees centigrade) yield 80 to 90 percent.

^1H NMR ($CDCl_3$): delta values 10.0 (s, 1H, COOH), 5.9 (m, 2H, HC=CH), 3.5 (m, 1H, CHCOO), 2.8 (m, 2H, C=CCH_2), 2.5 (m, 2H, CH_2).

EXAMPLE 2

Methyl 5-Oxocyclohex-2-ene-1-carboxylate

A solution of 0.7M diazomethane in ether was slowly added to a solution of 6.0 g (42.8 mmol) of 5-oxocyclohex-2-ene-1-carboxylic acid in 100 mL of ether at 0 degrees centigrade, with swirling. The addition of diazomethane was continued until the bubbling ceased and a yellow color persisted. The solution was treated with a rapid stream of nitrogen until the yellow color was discharged. The solvent was removed by evaporation. Benzene (100 mL) was added and evaporated at room temperature using an aspirator. The residue was placed on a vacuum line for 2 hours to produce 6.5 g (42.4 mmol, 99 percent) of methyl 5-oxocyclohex-2-ene-1-carboxylate (oil).

^1N NMR $CDCl_3$): delta values 5.9 (m, 2H, HC=CH), 3.7 (s, 3H, COOMe), 3.5 (m, 1H, HCOO), 2.9 (m, 2H, C=CCH_2), 2.7 (m, 2H, CH_2).

EXAMPLE 3

Methyl cis-5-Hydroxy-5-(trimethylsilylethynyl)cyclohex-2-ene-1-lcarboxylate

A solution of n-butyllithium (2.5 M, 16.8 mL, 42.1 mmol) was added dropwise, via a syringe, to a stirred solution of trimethylsilylacetylene (7 mL, 46.8 mmol) in 120 mL of tetrahydrofuran (THF) at −78 degrees centigrade. The resulting slurry was stirred at −78 degrees centigrade for 15 minutes and transferred via a cannula to slurry of 13.45 g (54.6 mmol) of cerium trichloride in 80 mL of THF at −78 degrees centigrade. The cerium chloride had been obtained by drying cerium trichloride heptahydrate (20.4 g, 54.6 mmol) at 140 to 160 degrees centigrade/0.1 mm Hg for 2 hours. Nitrogen was admitted to the cooled flask and 80 mL of dry THF was added to the resulting slurry, which was stirred overnight under nitrogen.

After the addition was complete (45 minutes), the resulting mixture was stirred for 1 hour at −78 degrees centigrade. The organocerium reagent, cerium dichloride trimethylsilylacetylide, was transferred over 45 minutes into a solution of 6.36 g (41.3 mmol) of methyl 5-oxocyclohex-2-ene-1-carboxylate in 80 mL of THF at −78 degrees centigrade. The resulting mixture was stirred for 1 hour more at −78 degrees centigrade and the reaction mixture was poured without warming into 400 mL of 10 percent ammonium chloride solution at 0 degrees centigrade. The resulting mixture was extracted with four 150-mL portions of ether. The combined organic extracts were washed with 200 mL of saturated

aqueous sodium chloride solution and dried over sodium sulfate. Evaporation of the solvent yielded 10.04 g (41.1 mmol, 99.5 percent) of methyl cis-5-hydroxy-5-(trimethylsilylethynyl)cyclohex-2-ene-1-carboxylate, an oil.

IR(CH_2Cl_2): 3585 (COH), 2160 (C≡C), 1721 ($COOCH_3$), 1653 (C≡C) cm^{-1}.

^{1}NRMCDCl_3): delta values 5.9–5.7 (m, 2H, CH=CH), 3.7 (s, 3H, $COOCH_3$), 3.3 (m, 1H, CHCOO), 2.6 (s, 1H, OH), 2.5 (dd, 1H, C=CCH_2), 2.4 (dd, 1H, C=CCH_2), 2.2 (m, 2H, CH_2), 0.2 (s, 9H, $Si(CH_3)_3$).

^{13}C NMR $CDCl_3$): delta values 174.0, 125.3, 123.4, 108.2, 87.4, 65.7, 51.9, 41.2, 39.1, 37.6.

MS, m/e (relative intensity): 252.21166 [M]+ (0.72), 237.0949 [M-CH_3]+ (29), 140.0657 (61). HRMS calcd for $Cl_3H_{20}O_3Si$: 252.1181.

Anal. Calcd for $C_{13}H_{20}O_3Si$: C, 61.86, H, 7.99. Found: C, 62.10, H, 8.13,

EXAMPLE 4

Methyl cis-(2,3-Epoxy-5-hydroxy)-5-(trimethylsilylethynyl)cyclohexane-1-carboxylate

A solution of tert.-butyl hydroperoxide (4.1 M, 0.85 mL, 3.4 mmol) in isooctane was added to a stirred mixture of molybdenum hexacarbonyl (10 mg, 0.07 mmol) and 0.1753 g (0.6946 mmol) of methyl cis-5-hydroxy-5-(trimethylsilylethynyl)cyclohex-2-ene-1-carboxylate in 10 mL of benzene. The mixture was then heated under reflux for 2 hours. The mixture cooled and was washed with three 10-mL portions of water. The combined aqueous layers were extracted with three 5-mL portions of methylene chloride and dried over sodium sulfate. Evaporation of the solvent gave 0.1805 g (97 percent) of an oil. Flash chromatography of the oil (4:1 hexanes-/ethyl acetate v/v) gave crystalline methyl cis-(2,3-epoxy-5-hydroxy)-5-(trimethylsilylethynyl)cyclohexane-1-carboxylate (0:131 g, 70 percent), mp. 74.1 to 74.6 degrees centigrade.

IR(KBr): 3360 (OH), 2160 (C≡C), 1732 (C=O), 1260, 845 cm^{-1}.

^{1}H NMR $CDCl_3$) 3.8 (s, 3H, $COOCH_3$), 3.5 (m, 1H, CHCOO), 3.3 (m, 2H, HCOCH), 2.4 (dd, 1H, CH_2), 2.3 (s, 1H, OH), 2.0 (d, 1H, CH_2), 1.85 (m, 2H, CH_2), 0.17 (s, 9H, C≡C$Si(CH_3)_3$).

^{13}C NMR $CDCl_3$) 172.45 (COO), 107.43 (SiC≡C), 89.47 (C≡C), 66.26, 52.2, 51.80, 50.71, 40.92, 38.26, 31.03, 0.20 ($Si(CH_3)_3$).

MS m/r (relative intensity): 253.0897 (21.8) [M-CH_3]+, 236.0871 (38.2) [M-CH_3OH]+, 191.0035 (19.3), 159.0715 (16.6). Calcd for $C_{13}H_{20}O_4Si$: 253.0896.

Anal. Calcd for $C_{13}H_2O_4Si$: C, 58,18, H, 7.51. Found: C, 58.09, H, 7.65.

EXAMPLE 5

Methyl cis-3,5-Dihydroxy-5-(trimethylsilylethynyl)cyclohex-1-ene-1-carboxylate.

A solution of 92.8 mg (0.345 mmol) of methyl cis-(2,3-epoxy-5-hydroxy)-5-(trimethylsilylethynyl)cyclohexane-1-carboxylate and 52.5 mg (0.345 mmol) of 1,8-diazabicylo-[5.4.0]-undec-7-ene in 10 mL of methylene chloride was stirred for 2 hours at room temperature. The solvent was removed by evaporation and the residue was dissolved in a minimum amount of methylene chloride and filtered through a plug of flash silica gel (1:1 hexanes/ethyl acetate v/v). Evaporation of the solvent yielded methyl cis-3,5-dihydroxy-5-(trimethylsilylethynyl)cyclohex-1-ene-1-carboxylate, a colorless oil, which crystallized on standing, mp 89.8 to 90.8 degrees centigrade.

IR (CH_2Cl_2): 3310 (OH, 2658 (C=C), 1721 ($COOCH_3$), 1653 cm^{-1}.

^{1}H NMR $CDCl_3$): delta values 7.1 (s, 1H, CCH), 4.4 (m, all couplings less than 2 Hz, 1H, CCH(OH)), 3.8 (s, 3H, $COOCH_3$), 3.0–3.4 (m, 1H, OH), 2.9–2.8 (dd, 2H, CH_2), 2.6 (s, 1H, OH), 2.5–2.2 (dd, 2H, CH_2), 0.17 (s, 9H, C-$CSi(CH_3)_3$).

^{1}H NMR (D_6DMSO): delta values 7.1 (s, 1H, C=CH), 6.2 (2,1H, OH), 5.6 (d, 1H, OH), 4.7 (bs, 1H, CCH(OH)), 4.0 (s, 3H, $COOCH_3$), 3.0 (d, J=17 Hz, 1H, C=CCH equatorial), 2.6 (d, J =17 Hz, 1H, C=CCH axial), 2.5 (m, 1H, (HO)CCH axial), 1.9 (dd, J=10, 10 Hz, 1H (HO)CCH axial).

^{13}C NMR $CDCl_3$): 167.20 (C=O), 138.88, 127.60, 108.0, 88.52, 66.04, 61.62, 51.92, 41.74, 38.87, 0.228.

Anal. Calcd for $C_{13}H_{20}O_4Si$: C, 58.18; H, 7.51. Found: C, 58.24; H, 7.65.

EXAMPLE 6

Addition of Nitromethane to Methyl cis-3,5-Dihydroxy-5-(trimethylsilylethynyl)cyclohex-1-ene-1-carboxylate

(i) Methyl cis-3,5-dihydroxy-5-trimethylsilylethynyl-cyclohex-1-ene-1-carboxylate (5.91 g, 22.0 mmol) was added in one portion to a mixture of nitromethane (12.2 g, 44.0 mmol) and DBU (6.7 g, 22.0 mmol) in 30 mL of dimethyl sulfoxide (DMSO). The mixture was stirred at room temperature for 15 hours and then neutralized to pH 6 with about 20 mL of 6 M HCl.

The resulting mixture was extracted with four 100-mL portions of ethyl acetate. The organic phase was washed with 30 mL of saturated aqueous sodium chloride solution and dried over sodium sulfate. Evaporation of the solvent gave a crude oil product (10.0 g), which contained some DMSO.

Flash chromatography in ethyl acetate/hexanes (3:7 v/v) gave methyl 3alpha,5alpha-dihydroxy-5beta-(trimethylsilylethynyl)-2alpha-nitromethylecyclohexane-1-beta-1-carboxylate (trans isomer, 0.8321g , 2.5 mmol , 11. 5 percent); methyl 3alpha,5alpha-dihydroxy-5beta-trimethylsilylethynyl-2beta-nitromethylcyclohexane-2beta-carboxylate (the cis isomer, 1.95 g, 5.9 mmol, 26.9 percent); methyl 3alpha, 5alpha-dihydroxy-5beta-ethynyl-2alpha-nitromethylcyclohexane-1beta-carboxylate (trans desilylated isomer, 1.52 g. 5.9 mmol, 26.9 percent); methyl 3alpha,5alpha-dihydroxy-5beta-ethynyl-2beta-nitromethylcyclohexane-1beta-carboxylate (cis desilylated isomer, 1.28, 5.0 mmol, 22 percent). The overall yield of nitro adducts was 88 percent.

(ii) Nitromethane (8 mL, 112 mmol) was added to a slurry of sodium hydride (2.4 g, 56 mmol, 50 percent in mineral oil) in 50 mL of dry DMSO. The mixture was cooled as necessary to maintain an internal temperature of 20 degrees centigrade and stirred slowly for 1 hour. Methyl c is-3,5-dihydroxy-5-(trimethylsilylethynyl)-cylohex-1-ene-1-carboxylate (3.0 g. 11.2 mmol) was added in one portion and the mixture was stirred for 24 hours at room temperature. To the resulting mixture was added 3 mL of conc HCl in ice. Additional HCl was added until the pH reached 7. The mixture was extracted with four 150-mL portions of ether, washed with 100 mL of saturated aqueous sodium chloride solution, dried over sodium sulfate and evaporated to

give 3.39 g of residue, which contained some DMSO (TLC).

Flash chromatography in ethyl acetate/hexanes (3:7 v/v) gave 2.12 g of product, characterized as a mixture of diastereomeric methyl 3,5-dihydroxy-5-(trimethylsilylethynyl)-2-nitromethylcyclohexane-1-beta-carboxylates.

Trans isomer (1.021 g, 25.8 percent), methyl 3alpha, 5alpha-dihydroxy-5beta-(trimethylsilylethynyl)- 2alpha-nitromethylcyclohexane-1betacarboxylate:

IR (CH_2Cl_2): 3421, 2958, 2161, 1737, 1558 cm^{-1}.

^1H NMR $CDCl_3$): delta values 4.7–4.6 (dd, 1H, CH_2NO_2), 4.0–4.1 (m, 1H, CHOH), 3.8 (bs, 2H, OH), 3.7 (s, 3H, $COOCH_3$), 2.8–2.9 (ddd, J =4, 12, 12 Hz, $CHCOOCH_3$) 2.5–2.6 (m, 1H, $CHCH_2NO_2$), 2.3–2.4 (m, 2H, CH_2 equatorial), 2.0 (dd, J =12, 12 Hz, 1H, CH_2 axial), 1.9 (dd, J =12, 3 Hz, 1H, CH_2 axial), 0.1 (s, 9H, $Si(CH_3)_3$).

^{13}C NMR ($CDCl_3$): delta values 173, 128, 106, 87, 75, 67.1, 66.8, 52, 41.5, 41.2, 36.7, 0.3.

Cis isomer (1.101 g, 19.8 percent), methyl 3alpha,5alpha-dihydroxy-5beta-(trimethylsilylethynyl)-2beta-nitromethylcyclohexane-1betacarboxylate:

IR (CH_2Cl_2) 3423, 2956, 2160, 1739, 1556 cm^{-1}.

^1H NMR $CDCl_3$): delta values 4.6 (dd, 1H, CH_2NO_2), 4.1 (m, 1H, CHOH), 3.7 (s, 3H, COOCH3), 2.9 (bs, 2H, OH), 2.0–2.2 (mc, 4H, CH_2), 0.2 (s, 9H, $Si(CH_3)_3$).

^{13}C NMR: delta values 173, 128, 106, 89, 74, 67.7, 67.1, 52, 41, 37, 30, 0.2.

Anal. Calcd for $C_{14}H_{22}O_6NSi$: C, 51.20, H. 6.75, N, 4.26. Found: C, 51.20; H, 7.19: N, 4.17.

EXAMPLE 7

Addition of Nitromethane to Methyl cis-(2,3-Epoxy-5-hydroxy)-5-(trimethylsilylethynyl)cyclohexane-1-carboxylate

Nitromethane (4.2 g, 68 mmol) was added to a solution of 50 mL of DMSO and 5.2 g, (34 mmol) of DBU in 50 mL of DMSO. The mixture was stirred for 5 minutes, after which 1.8 g (6.8 mmol) of solid methyl cis-2,3-epoxy-5-hydroxy-5-(trimethylsilylethynyl)cyclohexane-1-carboxylate was added in one portion. The reaction was followed by TLC, using 1:2 v/v ethyl acetate/hexanes as eluant. After 2 hours, all of the epoxide had been consumed and a new spot, corresponding to diol appeared. After 16 hours, TLC showed that four new products and no starting materials or diol was present.

The reaction mixture was poured into 100 mL of cold 5 percent HCl solution and extracted with four 50-mL portions of water and with 100-mL of saturated aqueous NaCl solution and dried over sodium sulfate. The ether was evaporated to yield 0.66 g of an oil, which was separated by flash chromatography (1:2 v/v ethyl acetate/hexanes) to yield methyl 3alpha, 5alpha-dihydroxy-5beta-(trimethylsilylethynyl)-2 alpha-nitromethylcyclohexane-1beta-carboxylate (0.28 g, 12.5 percent, trans nitro diol) and methyl 3alpha,5alpha-dihydroxy-5beta-(trimethylsilylethynyl)-2beta-nitromethylcyclohexane-1beta-carboxylate (0.31 g, 13.8 percent, cis nitro diol).

The aqueous phase was reextracted with methylene chloride and dried over sodium sulfate. Evaporation of solvent gave 0.52 g of an oil, separated by flash chromatography (1:1 v/v ethyl acetate/hexanes) into two desilylated nitroadducts, methyl 3alpha,5alpha-dihydroxy-5beta-ethynyl-2alphanitromethylcyclohexane-1beta-carboxylate (0.25 g, 12.4 percent, trans desilylated isomer) and methyl 3alpha, 5alpha-dihydroxy-5beta-ethynyl-2beta-nitromethylcyclohexane-2beta-carboxylate (0.19 g, 9.4 percent, cis desilylated isomer).

EXAMPLE 8

Acetonide of Methyl 3alpha,5alpha-Dihydroxy-5 beta-(trimethylsilylethynyl)-2alpha-nitromethylcyclohexane-1beta-carboxyate

A mixture of 2-methoxypropene (260 microL, 3.6 mmol), trans nitro diol (methyl 3alpha,5alphadihydroxy- 5beta-(trimethylsilylethynyl)-2alpha-nitromethylcyclohexane-1beta-carboxylate, 1.2 g, 3.6 mmol) and pyridinium tosylate (10 mg, 0.036 mmol) in 100 mL of benzene was stirred for at room temperature for 15 minutes. After 260 microL (3.6 mmol) of additional 2-methoxypropene was added, the resulting mixture was heated under reflux for 5 minutes. The resulting solution was cooled and washed with 30 mL of saturated aqueous sodium bicarbonate solution with 30 mL of saturated aqueous sodium chloride solution and dried over sodium sulfate. Evaporation of solvent yielded 1.22 g (3.22 mmol, 89 percent) of acetonide as an oil.

IR (neat ATR): 2990, 2164, 1735, 1556 cm^{-1}.

^1H NMR $CDCl_3$) delta values 4.6–4.5 (dd, 1H, $CHNO_2$), 4.4–4.35 (dd, 1H, $CHNO_2$), 4.25–4.3 (m, 1H, CHOC), 3.7 (s, 3H, $COOCH_3$), 3.0 (ddd, J =3, 4, 15 Hz, 1H, CH equatorial), 2.85 (ddd, J =5, 12, 12 Hz, 1H, $CHCOOCH_2$), 2.6 (m, 1H, $CHCH_2NO_2$), 2.4 (ddd, J =3, 5, 15 Hz, 1H, CH equatorial), 1.8 (m, 2H, CH axials), 1.6 (s, 3H, CH_3), 1.4 (s, 3H, CH_3), 0.16 (s, 9H, $Si(CH_3)_3$).

^{13}C NMR $CDCl_3$): delta values 173.6, 106.3, 97.9, 88.5, 75.2, 66.3, 65.4, 52.0, 41.8, 41.5, 38.7, 33.0, 31.4, 30.3, 0.3.

HRMS, m/e (relative intensity): 354.1366 $[M-CH_3]^+$ (11 3), 294.1158 $[M-OC_3\ H_6]^+$ (5.4), 264.1184 $[294-NO_2]^+$ (46.5), 73.0472 $[TMSi]^+$ (100); calcd for $C_{16}H_{24}NO_6Si$ 354.1373.

EXAMPLE 9

Oxidation of 1-hydroxy-5-methoxy-naphthalene to 1,4-dihydro-4,4,5-trimethoxy-1-oxonaphthalene by Iodobenzene Diacetate

A solution of 15.5g (48 mmol) of iodobenzene diacetate and 22g of $NaHC_3$ in 100 mL of methanol/-trimethyl orthoformate (1/1) was stirred at room temperature for 30 minutes. To this mixture a solution of 3.74g of 1-hydroxy-5-methoxynaphthalene (21.5 mmol) in 250 mL of methanol was added dropwise. The color of the mixture changed from orange to greenish yellow over 2 hours at room temperature.

Ether (150 mL) was added to the mixture, and then sat. $NaHCO_3$ (75 mL). The aqueous washings were back extracted with ether (75 mL×3). The combined ethereal extracts were washed with saturated aqueous sodium chloride solution and dried over sodium sulfate. The solution was evaporated to give 1,4-dihydro-4,4,5-trimethoxy-1-oxonaphthalene.

Flash chromatography of this product with elation using EtOAc:Hex 1:1 yielded 3.70g (74 percent) of crystals of 1,4-dihydro-4,4,5-trimethoxy-1-oxonaphthalene, mp 62–63 degrees centigrade.

^1H NMR ($CDCl_3$): delta values 7.7 (d, 1H, aromatic), 7.52 (t, 1H, aromatic), 7.16 (d, 1H, aromatic), 6.80 (m,

2H, HC=CH), 3.92 (s, 3H,OCH_3), 3.14 (s, 6H, $(OCH_3)_2$) (2 OCH_3).

UV (MeOH): maximum wavelength: 222 nm.

IR (neat): 1672, 1635, 1589, 1580, 1300, 1178, 1068, 1031 cm^{-1}.

EXAMPLE 10

3-[(2beta-Carbomethoxy-4beta-ethynyl-4alpha-6alpha-(di-O-isopropylidenyl)-cyclohexanyl-1-yl)]nitromethyl-4,4,5-trimethoxy-1-oxo-1,2,3,4-tetrahydronaphthalene

A solution of 0.904 g (3.0 mmol) of trans nitroacetonide (acetonide of methyl 3alpha, 5alpha-dihydroxy-5beta-(trimethylsilylethynyl)-2alpha-nitromethylcyclohexane-1beta-carboxylate), 1.34 g (5.7 mmol) of 1.4-dihydro-4,4,5-trimethoxy-1-oxonaphthalene and 750 microL (5 mmol) of DBU in 0.5 mL of acetonitrile was stirred for 5 days at room temperature. Methylene chloride (5 mL) was added to the mixture and the solution was chromatographed on a column packed with 150 g of silica gel (5 cm column, 30:70 v/v ethyl acetate/hexanes slurry). The material on the column was eluted with 400 mL of 30:70 v/v ethyl acetate/hexanes. After the nitro acetonide was eluted, as followed by TLC (iodine development), the chromatographic separation was continued with 1000 mL of 50:50 v/v ethyl acetate/hexanes.

Evaporation of the solvent from the various fractions gave recovered nitro acetonide (0.66 g, 2.2 mmol), recovered dimethyl ketal (1.03 g, 4.4 mmol) and product, 3-[(2beta-carbomethoxy-4beta-ethynyl-4alpha,6alpha-(di-O-isopropylidenyl)cyclohexanyl-1-yl)-nitromethyl]-4,4,5-trimethoxy-1-oxo-1,2,3,4-tetrahydronaphthalene (0.274 g, 0.51 mmol, 62 percent based on recovered acetonide) as an oily mixture of diasteromers.

IR (ATR thin film): 1733 (COOMe), 1686 (C=O), 1588, 1579 (NO_2) cm^{-1}.

^1H NMR ($CDCl_3$): delta values 7.6 (d, 1H, Ar), 7.4 (dd, 1H, Ar), 7.1 (d, 1H, Ar), 5.3-5.0 (d, 1H, $CHNO_2$), 4.4-4.0 (m, 1H, CHOC), 3.7 (s, 3H, $ArOCH_3$), 3.5 (s, 3H, $COOCH_3$), 3.3-2.8 (complex group of overlapping protons, 10H), including ($COCH_3$ ketal, 3.2, 3H, and 3.1, 3H), (O=CCH_2, 2H), and ($CHCOOCH_3$, 1H), ($HCCHNO_2$, 1H)), 2.5 (s, 1H, C≡CH), 2.5 (d, 1H, CH_2), 2.2 (d, 1H, CH_2), 1.8 (d, 1H, NO_2CHCH), 1.6-1.5 (m, 2H, CH2 , 1.5 (s, 3H, CCH_3), 1.2 (s, 3H, CCH_3).

^{13}C NMR ($CDCl_3$): mixture of two distereomers, (195.4, 195.1), (174.3, 173.2), (157.6, 157.5), (134.3, 134.0), (130.3, 130.2), (125.3), (120.05, 120.0), (117.2, 117.15), (101.6, 101.6), (97.9, 97.7), (86.1, 85.10), (84.48, 84.42), (72.6, 72.5), (66.0, 65.9) (64.5, 64.4), (55.9), (52.2, 51.6), (50.56, 50.46), (50.4, 50.1), (43.4 43.1), (42.8, 42.7), (42.0, 40.7), (39.77, 39.70), (35.8, 35.6), (32.7, 32.6), (31.2, 31.1), (30.05, 29.9).

EXAMPLE 11

9beta-Ethynyl-5,5-dimethoxy-12-hydroxy-7alpha, 9alpha-di-(O-isopropylidenyl)-4-methoxy-6-nitro-5, 5a,6,6a,7,8,9,10,10a-decahydro-11-naphthacenone

Sodium hydride (64 mg, 1.4 mmol) was added in one portion to a solution of 3-[(2beta-carbomethoxy-4beta-ethynyl-4alpha,6alpha-(di-O-isopropylidenyl)cyclohexanyl-1-yl)]-nitromethyl-4,4, 5-trimethoxy-1-oxo- 1,2,3,4-tetrahydronaphthalene (0.377 g, 0.7 mml) and methanol (80 drops) in 25 mL of toluene at 0 degrees centigrade. After 15 minutes' stirring, the cooling bath was removed. The reaction mixture was stirred for an additional 4 hours at room temperature and then washed briefly with 10 mL of cold 5 percent HCl. The organic phase was further washed with 5 mL of saturated aqueous sodium bicarbonate solution, with two 10-mL portions of saturated aqueous sodium chloride solution and dried over sodium sulfate. The solvent was evaporated to give 0.372 g of crude oily product, which was flash chromatographed (30:70 v/v ethyl acetate/hexanes, then 50:50 ethyl acetate/hexanes) to yield 0.212 g (0.42 mmol, 59.8 percent) of 9beta-ethynyl-5,5-dimethoxy-12-hydroxy-7alpha,9alpha-(di-O-isopropylidenyl)-4-methoxy-6-nitro-5,5a,6,6a,7,8,9,10,10a, 11-decahydro-11-naphthacenone, white crystalline solid, mp 234 degrees centigrade (decomp).

IR (ATR thin film): 3320 (C=C-OH), 2260 (C≡CH), 1559 (NO_2) cm^{-1}.

^1H NMR ($CDCl_3$): delta values 16.2 (s, 1H, C=COH), 7.8 (d, 1H, ArH), 7.1 (d, 1H, ArH), 5.2 (dd, J =1, 3 Hz, 1H, $CHNO_2$), 4.6 (d, J =4.5 Hz, 1H, CHOC), 3.9 (s, 3H, $ArOCH_3$), 3.9 (ddd, J =4.5, 13, 13 Hz, 1H, 0=CCH), 3.5 (d, J =4.5 Hz, 1H, C=C—CHC-HNO_2), 3.4 (s, 3H, OCH_3 ketal), 3.1 (ddd, 1H, CH_2 equatorial), 3.0 (s, 3H, OCH_3 ketal), 2.9 (ddd, J =3, 3, 13 Hz, 1H, CH2 equatorial), 2.5 (s, 1H, C≡CH), 1.8 (d, J =12 Hz, 1H, $NO_2CHCHCO$), 1.67 (d, 1H, CH_2 axial), 1.64 (s, 3H, $OCCH_3$), 1.5 (dd, J =12, 12 Hz, 1H, CH_2 axial), 1.3 (s, 3H, $OCCH_3$).

^{13}C NMR ($CDCl_3$): HETCOR-DEPT 196.9 (C=O), 172.6 (ArC=COH), 157.2 (ArC=COH), 133.0 (Ar), 130.6 (ArH), 122.8 (Ar), 119.4 (ArH), 115.7 (ArH), 101.6, 101.3, 98.4, 85.2 (C≡CH), 79.9, 72.1 ($CHNO_2$), 69.5 (CHOC), 66.3, 55.8 ($ArOCH_3$), 52.5 ($COCH_3$), 51.4 ($COCH_3$), 46.0 (NO_2CCHCO), 44.8 ($CHCNO_2$), 40.2 (CH_2), 35.3 (CHC=O), 34.3 (CH_2), 30.8 ($OCCH_3$), 30.4 ($OCCH_3$).

UV-Vis: maximum wavelengths: 346, 341, 230 nm.

EXAMPLE 12

9beta-Acetyl-7alpha,9alpha,12-trihydroxy-4,5-dimethoxy-6-nitro-6,6a,7,8,9,10,10a,11-octahydro-11naphthacenone

Sulfuric acid (1.5 mL, 3M) was added to a solution of 212 mg (0.42 mmol) of 9beta-ethynyl-5,5-dimethoxy-12-hydroxy-7alpha,9alpha-(di-O-isopropylidenyl)-4-methoxy-6-nitro-5,5a,6,6a,7,8,9, 10,10a,11-decahydro-11-naphthacenone in 20 mL of THF. The solution immediately turned a bright yellow color. To the resulting solution was added 24.5 mg (0.11 mmol) of HgO. The resulting mixture was stirred for 4 hours at room temperature, cooled to 0 degrees centigrade and neutralized to pH 6 with 0.5 g of potassium hydroxide in 3 mL of water. The mixture was poured into 20 mL of water and extracted with four 20-mL portions of ethyl acetate. The combined organic layers were washed with two 20-mL portions of water and with 20 mL of saturated aqueous sodium chloride solution and dried over sodium sulfate. The solvent was removed by evaporation to yield 0.176 g (0.39 mmol, 93.2 percent) of 9beta-acetyl-7alpha,9alpha,12-trihydroxy-4,5-dimethoxy-6-nitro-6,6a,7,8,9,10,10a, 11-octahydro-11-naphthacenone, yellow solid. Product recrystallized from acetone gave fine yellow needle crystals, mp 186 degrees centigrade (decomp).

IR (ATR thin film): 3427 (OH), 1711 (C=O), 1628, 1591, 1554 (NO_2) cm^1.

^1H NMR (THF D_4): delta values 14.3 (s, 0.5H, ArOH), 8.0 (d, 1H, ArH), 7.5 (dd, 1H, ArH), 7.2 (d, 1H, ArH),m 6.4 (d, 1H, $CHNO_2$), 5.5 (bs, 0.5H, OH), 5.0 (bs,

0.5H, OH), 4.6 (m, 1H, CHOH), 3.9 (s, 2H, $ArOCH_3$ D-ring), 3.7 (s, 3H, $ArOCH_3$ C-ring), 3.7 (ddd, 1H, COCH), 2.6 (ddd, 1H, CH_2 equatorial), 2.5 (ddd, 1H, CH2 equatorial), 2.3 (s, 3H, $COCH_3$), 1.8 (m, 1H, NO_2CHCH), 1.8–1.7 (m, 2H, CH2 axials partly obscured by THF peak).

^{13}C NMR (THF D_4): delta values 211.3 (C=O), 206.7 (C=O), 160.0, 157.3, 128.5, 122.4, 117.6, 117.5, 112.5, 112.4, 110.1, 81.9, 80.4, 69.87, 69.83, 62.7, 56.6, 46.0, 39.1, 36.2, 35.9, 35.8.

UV-Vis (MeOH) maximum wavelengths: 339, 321, 262, 220 nm.

EXAMPLE 13

9beta-Acetyl-7alpha,9alpha-dihydroxy-4-methoxy-6-nitro-5,6,6a,7,8,9,10,10a,11,12-decahydro-5,11-12-naphthacenetrione

Thallium nitrate (55 mg, 0.11 mmol) was added to a solution 50 mg (;0.11 mmol) of 9beta-acetyl-7alpha,9alpha,12-trihydroxy-4,5-dimethoxy-6-nitro-6,6a,7,8,9,10,-10a, 11-octahydro-11-naphthacenone in 5 mL of acetone at 0 degrees centigrade. The mixture was brought to room temperature and stirred for 2 hours. Additional thallium trinitrate (11 mg, 0.02 mmol) was added and stirring was continued for 1 hour. The resulting solution was poured into 20 mL of water and extracted with three 25-mL portions of ethyl acetate. The combined organic extracts were washed with two 25mL portions of water and with 25 mL of saturated aqueous sodium chloride solution and dried over sodium sulfate. The solvent was evaporated to yield 99.5 mg of crude yellow product, an orange solid.

The product, which turned black upon standing, was dissolved in 5 mL of 9:1 ethyl acetate/hexanes v/v. After 16 hours, an orange precipitate had formed. The supernatant was removed by decantation and the resulting solids dried to give 25 mg (0.06 mmol, 54.5 percent) of 9beta-acetyl-7alpha,9alpha-dihydroxy-4-methoxy-6-nitro-5,6,6a,7,8,9,10,10a,11,12-decahydro-5,11,12-naphthacenetrione, mp 242 degrees centigrade (decomp).

^1H NMR (acetone D_6): delta values 7.9 (dd, 1H, aromatic), 7.7 (d, 1H, aromatic), 7.6 (d, 1H, aromatic), 6.2 (d, J =4.5 Hz, 1H, $CHNO_2$), 5.5 (s, 0.5, OH), 4.9 (m, 0.5, OH), 4.7 (m. 1H, CHOH), 4.0 (s, 3H, $ArOCH_3$), 3.5 (ddd, J =4, 12, 13, Hz, 1H, $COCHCH_2$), 2.8 (ddd, J =1, 5, 13 Hz, 1H, $COCHCH_2$ equatorial), 2.4 (ddd, 1H, $COHCH_2$ equatorial), 2.3 (s, 3H, $COCH_3$), 1.9 (m, 1H, NO_2 CHCH partially obscured by acetone quintet).

IR (ATR thin film): 1709 (C=O), 1663, 1665, 1587, 1560 (NO_2) cm^{-1}.

UV-Vis (MeOH) maximum wavelengths: 424 nm 274, 258 nm.

EXAMPLE 14

7alpha,9alpha-(Di-O-isopropylidenyl)-4,5-dimethoxy-9beta-ethynyl-12-hydroxy-6-nitro-6,6a,7,8,9,10,10a, 11-octahydro-11-naphthacenone

A catalytic amount of pyridinium tosylate (5 mg) was added to a solution of 100 mg (0–20 mmol) of the decahydro-11-naphthacenone (example 11) in 20 mL of CH_2Cl_2. The mixture was refluxed for 6 hours while the color of the solution changed from light to shiny yellow. The reaction mixture was washed with water (2×20 mL) dried over Na_2SO_4 and the solvent was removed in vacuo. The yellow residue was recrystallized from hexane: ethyl acetate (9:1) to give the octahydro-11-naphthacenone as a mixture of 2 stereoisomers at C_6 (88 mg, yield 94 percent). The isomer can be separated by chromatography. Major isomer 85 percent m.p. 243–244 degrees centigrade.

IR (KBr) 3262, 1733, 1616, 1572, 1563, 1554, 1501, 1456, 1430, 1382, 1276, 1261, 1215 cm^{-1}.

NMR (360 MHz, $CDCl_3$): major isomer 14.01(s, 1H), 8.12(d, 1H), 7.49(t, 1H), 7.72(d, 1H), 6.35(d, J =4 H_2lH), 4.73(d, 1H), 3.95(s, 3H), 3.27(m, 1H), 2.16(d, 1H), 1.61(s, 3H), 1.30(s, 3H), ppm.; (minor isomer 15 percent) 13.34(s, 1H), 8.05(d, 1H), 7.47(t, 1H), 7.05(d, 1H), 6.21(d, J 10.4 H_2lH), 4.40(d, 1H), 3.91(s, 3H), 3.71(s, 3H), 3.66(d, 1H), 3.12(m, 2H), 2.53(s, 1H), 2.19(m, 2H), 1.67(s, 3H), 1.37(s, 3H) ppm.

UVVisi (MeOH) maximum wavelength: 230, 266, 328, 396 nm.

Anal. Calcd. for $C_{25}H_{25}O_8N$: C, 64.2, H, 5.39, N, 3.00. Found: C, 64.9, H, 5.31, N: 3.04.

EXAMPLE 15

7alpha-9alpha-(Di-O-isopropylidenyl)-9beta-ethynyl-11-hydroxy-4-methoxy-6-nitro-7,8,9,10-tetrahydro-5, 12-nathacenedione

A solution of 36 mg (0.075 mmol) of the octahydro-11-naphthacenone and 60 mg (0.675 mmol) of $NaHCP_3$ in 10 mL of acetone was treated with a solution of 167 mg (3mmol) of cerium ammonium nitrate (CAN) and 1 mg of dichlorodicyanobenzoquinone (DDQ) in 2 mL of acetone added in one portion at 0 degrees centigrade. The reaction mixture was stirred at room temperature for 1.5 hours during which the color changed from shiny yellow to orange red, and then 25 mL of CH_2Cl_2 was added. The mixture was filtered through over Celite. The organic layer was washed with saturated NaCl solution (2×20 mL), dried over Na_2SO_4, and evaporated to give the tetrahydro-5,12-naphthacenedione as a red crystals (29 mg, 86 percent).mp greater than 258 degrees centigrade (decomp).

IR (KBr) 3306, 1620, 1588, 1529, 1491, 1369 cm−.

^1H NMR (360 MHz, CD_2Cl_2 15.00(s, 1H), 7.57(t, 1H), 7.36(d, 1H), 4.50(m, 1H), 4.00(s, 3H), 3.12(m, 2H), 2.65(m, 2H), 2.57(s, 1H), 1.68(s, 3H), 1.37(s, 3H) ppm.

UV - Vis. (MeOH) maximum wavelength: 223, 240, 248, 358, 440 nm; ($CHCl_3$) 246, 370, 390, 416, 436 nm.

EXAMPLE 16

6-Desoxy-6-nitrodaunomycinone

A solution of 12 mg of (0.027 mmol) of the tetrahydro-5,12,-naphthacenedione in 2.5 mL of tetrahydrofuran was treated with 150 microL of H_2SO_4(3M) and then 5 mg of mercuric oxide at 0 degrees centigrade and stirred at room temperature for 24 hours. The turbit solution was neutralized with $NaHCO_3$ to pH 8, and extracted with CH_2Cl_2 (10 ×) 15 mL). The extract was dried over Na_2SO_4, and evaporated to yield 6-desoxy-6-nitrodaunomycinone as a red sol id (7 mg , 61.4 percent) . Flash chromatography on silica (60–200 mesh) eluting with 70:25:5(ethyl acetate:hexane:MeOH) afforded 2 mg of the pure mycinone as red crystals.

IR (CHC13), 3364, 1708, 1662, 1615, 1591, 1525, 1499, 1446, 1278, 1336 cm−.

^1H NMR (360) MHz, CD_2Cl_2 15.15(s, 1H), 8.06 (d, 1H), 7.82(t, 1H), 7.42(d, 1H), 5.44(m, 1H, OH), 4.61(s, 1H), 4.09(s, 3H), 3.79(m, 1H, OH), 3.21(d, 1H), 3.00(d, 1H), 2.40(s, 3H), 2.30(d, 1H), 2.21(m, 1H) ppm.

UVVisi maximum wavelengths: (CHC13) 245, 250, 420, 446 nm; (MeOH) 360, 385, 418, 441, 466 nm.

EXAMPLE 17

6-Amino-9beta-ethynyl-4-methoxy-7alpha,9alpha,11-trihydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione

A solution of 15 mg (0.033 mmol) of 6-desoxy-6-nitrodaunomycinone and 96 mg (0.70 mmol) of $NaOOCCH_3;3H_2O$ in 2 mL of CH_3OH was treated with $SnCl_2H_2O$ (183 mg, 0.88 mmol), in 3 portions over a 90 min. at room temperature. During the addition the color of the solution changed to yellow. After the $SnCl_2$ was added, the mixture was stirred for 1 h, and the solvent was evaporated. A mixture of 15mL of CH_2Cl_2 and 15mL of saturated aqueous $NaHCO_3$ was added and the mixture was stirred for 30 min. During the stirring the color changed to pink and CO_2 was evolved.

The mixture was filled through Celite and extracted with CH_2Cl_2(3×20mL). The combined organic layers were washed with saturated aqueous NaCl, dried (Na_2SO_4), and evaporated to yield 14 mg of yellow solid. TLC showed that this was a mixture of 2 compounds. Flash chromatography using elution with hexane: ethyl aceate: MeOH(75:20:5) gave two compounds, the 6-desoxy-6-nitro starting material (6mg), and 6-amino-9beta-ethynyl-4-methoxy-5,7alpha,9alpha,11,12-pentahydroxy-7,8,9,10-tetrahydronaphthacene (7.5mg) as shining yellow crystals (mp, 234–238 degrees centigrade).

NMR: 14.1(s, 1H,OH)0),13.4(s,2H,OH),8.1(d,1H), 7.7(t,1H),7.2(d,1H),5.0(m,1H),4.25(m,1H,OH),4.04(s, 3H),3.62(m,2H,NH_2),3.15(m1H,OH),2.95(q,2H), 2.55(s, 1H,C═CH),1.96(m,2H).ppm.

FT-IR (KBr) 3647, 3375,3289, 1671, 1634, 1601, 1582 cm^{-1}.

UV-Vis ($CHCl_3$) maximum wavelengths 446,422,274,250 nm.

A saturated solution of 17.5 mg (0.032 mmol) ceric ammonium nitrate in acetone was added at 0 degrees centigrade to pentahydroxynaphthacene (7mg, 0.016 mmol) and $NaHCO_3$(10mg) in 2 mL of acetone. The reaction mixture was stirred for 5 h at room temperature and then filtered through Celite and extracted with CH_2Cl_2 (7×10mL). Evaporation yielded 7 mg of the amino trihydroxy-5,12-naphthacenone as purple red crystals.

^1H NMR (CD_2Cl_2), 14.80(s,1H,OH), 8.10 (d,1H), 7.85(t,1H),7.42(d,1H),5.35(d,1H),4.30(d,1H,OH), 4.09 (s,3H),3.57(m,2H),3.35(m,1H,OH),3.15(m,2H),2.55(s, 1H),1.95(m,2H)ppm.

UV-Vis ($CHCL_3$) maximum wavelength: 498, 442, 313, 269 nm.

FT-IR(KBr) 3644, 3277, 1671, 1631, 1580 cm^{-1}.

EXAMPLE 18

Daunomycinone

A solution of 7 mg (0.018 mmol) of the amino-5,12-naphthacenedione and 1 mg of pyridinium tosylate in 2mL of dimethoxyethane was treated with 15 microL of isoamylnitrite. As the mixture was stirred at room temperature a purple precipitate formed, and 0.5mL of 0.01N HCL was added, after stirring had been continued for 5 h, the visible spectrum of the mixture showed absorption at 515 nm. Then HgO (40 mg, 0.18mmol), was added and stirring was continued for 24 h. The mixture was filtered through Celite, extracted with CH_2Cl_2 (15×10mL) and evaporated to yield 10 mg of red solid. Flash chromatogrphy with elution with ethyl acetate:hexane:MeOH ((90: 5:5), followed by recrystalization from $CHCl_3$ gave 3 mg of daunomycinone (mp 217–221 degrees centigrade).

^1H-NMR (CD_2Cl_2, 360 MHz) , 14.22 (s , 1H) , 13.47(2,1H), 8.21(d,1H), 8.00 (t,1H), 7.61 (d,1H), 5.48 (m,1H), 4.23 (s,3H), 4.07 (s,3H), 3.95 (d, 1H), 3.10 (m,2H), 2.57 (s,3H), 2.30 (m,2H) ppm.

FT-IR (CH_2Cl_2) 3540, 3053, 2927, 1712, 1616, 1578, 1420 cm^{-1}.

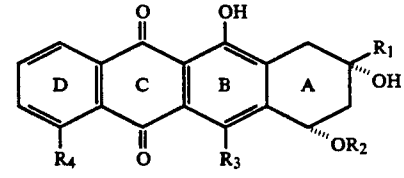
UV-Visi (MeOH) maximum wavelength: 532, 495, 476, 287, 253, 234nm.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

Although preferred embodiments of the invention have been described with some particularity, many modifications and variations in the preferred embodiment are possible without deviating from the invention. Is it therefore to be understood that, within the scope of the appended claims, the invention may be practiced other than as specifically described.

What is claimed is:

1. A process for the production of a compound of the general formula:



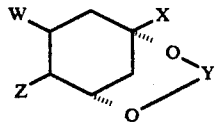
2

wherein R_1 is one of: O═CCH$_3$ or O═C—CH$_2$OH;
R_2 is one of daunosamine, or H;
R_3 is NO_2; and
R_4 is OCH_3, OH or H;
comprising the steps of:
preparing a mono ketal of a 1,4-naphthoquinone as the precursor of the CD rings;
preparing a precursor for Ring A with C_6 and C_{11} attached and the stereochemistry at C_7 and C_9 established and coupling it to CD and then completing ring B;
said step of preparing a precursor for Ring A comprising the substeps of methylation of 5-oxocyclohex-2-enecarboxylic acid to methyl 5-oxocyclohex-2-enecarboxylate at a reaction temperature of between −20 to 20 degrees centigrade, trimethylsilylethynylation of said cyclohexenecarboxylate at a temperature of between −50 to −78 degrees centigrade after removal of water and ethanol to produce methyl cis-5-hydroxy-5-(trimethylsilylethynyl)cyclohex-2-enecarboxylate, epoxidation to methyl cis-(2,3-epoxy-5-hydroxy)-5-(trimethylsilyl ethynyl)cyclohexane-1-carboxylate and opening of the resulting epoxide ring to give methyl cis-3,5-dihydroxy-5-(trimethylsilylethynyl) cyclohex-1-ene carboxylate.

2. A process according to claim 1 in which the mono ketal of 1,4-naphthoquinone is the 4-mono ketal of juglone methyl ether.

3. A process for the production of daunomycinone and related compounds in accordance with claim 1 in which the precursor for the A ring, with C_6 and C_{11}

attached and the stereochemistry at C_7 and C_9 established, has the general structure:



wherein W is an ester or similar group capable of acting as an electron pair acceptor in a Claisen condensation and related reactions;

X is an umpolung equivalent of an acetyl group such as acetylide, trimethylsilylacetylide, ethyl or methyl vinyl ether, 2-methyl-1,3-dithiane or corresponding dithioacetal or dithioacetal oxide, or cynaohydrin silyl ether or related compounds;

Y is 2H, or if needed, a suitable protecting group for a 1,3 diol, such as a cyclic ketal e.g. acetonide or a cyclic ester e.g. boronate or carbonate;

Z is a one carbon umpolung of carbonyl such as nitromethyl, 1,3-dithiane or the corresponding sulfoxide of the 1,3-dithiane, a cyanohydrin silyl ether or related compounds.

4. A process for the production of daunomycinone, comprising the steps of:

methylation of 5-oxocyclohex-2-enecarboxylic acid to methyl 5-oxocyclohex-2-enecarboxylate at a reaction temperature of between −20 to 20 degrees centigrade, trimethylsilylethynylation of said oxocyclohexenecarboxylate at a temperature of between −50 to −78 degrees centigrade after removal of water and ethanol to produce methyl cis-5-hydroxy-5-(trimethylsilylethynyl)cyclohex-2-enecarboxylate, conversion to an epoxide and opening of the resulting epoxide ring to give methyl cis-3,5-dihydroxy-5-(trimethylsilyl)ethynylcyclohex-1-enecarboxylate;

addition of nitromethane to the said dihydroxyethynyl ester to give methyl 3alpha,5alpha-dihydroxy-5beta-(trimethylsilylethynyl)-2alpha-nitromethylhexane-1beta-carboxylate;

formation of the acetonide of methyl 3alpha,5alpha-dihydroxy-5-beta-(trimethylsilylethynyl)-2alpha-nitromethylcyclohexane-1-beta-carboxylate;

condensation of the said acetonide with 1,4-dihydro-4,4,5-trimethoxy-1-oxonaphthalene in the presence of 1,8-diazabicyclo[5.4.0 undec-7-ene in an aprotic solvent to produce 3-[2beta-carbomethoxy-4beta-ethynyl-4alpha,6alpha-(di-O-isopropylidenyl)cyclohexan-1alpha-yl]-nitromethyl-4,4,5-trimethoxy-1-oxo-1,2,3,4-tetrahydronaphthalene;

cyclizing said 1-oxotetrahydronaphthalene to produce 7alpha,9alpha-(di-O-isopropylidenyl)-9beta-ethynyl-12-hydroxy-6-nitro-4,5,5-trimethoxy-5,5a,6, 6a,7,8,9,10,10a,11-decahydro-11-naphthacenone;

converting said decahydro-11-naphthacenone to 7alpha,9alpha-(di-O-isopropylidenyl)-4,5-dimethoxy-9beta-ethynyl-12-hydroxy-6-nitro-6,6a,7,8,9,10,-10a,11-octahydro-11-naphthacenone;

oxidizing said octahydro-11-naphthacenone to 7alpha,9alpha-(di-O-isopropylidenyl)-9beta-ethynyl-11-hydroxy-4-methoxy-6-nitro-7,8,9,10-tetrahydro-5,12-naphthacenedione;

hydrolysing said 5,12-naphthacenedione to 6-desoxy-6-nitrodaunomycinone;

reducing said nitrodaunomycinone to 6-desoxy-6-aminodaunomycinone;

converting said aminodaunomycinone to the 6-diazoniumdaunomycinone and from this obtaining daunomycinone, 6-desoxydaunomycinone, the 6-desoxy-6-halodaunomycinones, 6-desoxy-6-cyanodaunomycinone and other 6-analogues easily derived from these products.

5. The process of claim **4**, wherein the aprotic solvent for condensing the acetonide with 1,4-dihydro-4,4,5-trimethoxy-1-oxonaphthalene can be acetonitrile, dimethylsufoxide, NNdimethylpropyleneurea or hexamethylphosphoramide.

6. The process of claim **4**, wherein the aprotic solvent for condensing the acetonide is acetonitrile.

7. The process of claim **4**, wherein said 1-oxotetrahydronaphthalene is cyclized with an alkali metal alkoxide of 1–6 carbon atoms.

8. The process of claim **7**, wherein said alkali metal alkoxide is sodium methoxide produced by potassium or sodium hydride and a catalytic quantity of methanol in toluene or other aprotic solvent.

9. The process of claim **4**, wherein said decahydro-11-naphthacenone is converted to 7alpha,9alpha-(di-O-isopropylidenyl)-4,5-dimethoxy-9beta-ethynyl-12-hydroxy-6-nitro-6,6a,7,8,9,10,10a,11-octahydro-11-naphthacenone under acidic conditions.

10. The process of claim **4**, wherein said decahydro-11-naphthacenone is converted into said octahydro-11-naphthacenone by treatment with pyridinium tosylate.

11. The process of claim **4**, wherein said octahydro-11-naphthacenone is oxidized to 7alpha, 9alpha-(di-O-isopropylidenyl)-9beta-ethynyl-11-hydroxy-4-methoxy-6-nitro-7,8,9,10-tetrahydro-5,12-naphthacenedione with reagents such as cerium ammonium nitrate or thallium trinitrate or iodobenzenediacetate using with each oxidant a catalytic quantity of 2,3-dichloro-5,6-dicyanobenzoquinone.

12. The process of claim **4**, wherein the said di-O-isopropylidenylethynyltetrahydro-5,12-naphthacenedione is hydrolysed by acid in the presence of mercuric oxide to 6-desoxy-6-nitrodaunomycinone.

13. The process of claim **4**, wherein the said nitrodaunomycinone is reduced to 6-amino-6-desoxydaunomycinone using $SnCl_2$ in the presence of sodium acetate in methanol.

14. The process of claim **4**, wherein the said aminodaunomycinone is converted via a diazonium intermediate into one of daunomycinone, 6-desoxydaunomycinone, the 6-desoxy- 6-halodaunomycinones, 6-desoxy-6-cyanodaunomycinone and compounds easily derived from these products.

15. The process of claim **14**, wherein said diazonium compound is formed from the amino daunomycinone in 1,2-dimethoxyethone using amyl nitrite in the presence of pyridinium tosylate.

16. The process of claim **4** wherein said decahydro-11-naphthacenone is hydrolyzed by HgO in the presence of acid to form 9beta-acetyl-4,5-dimethoxy-6-nitro-7alpha,9alpha, 12-trihydroxy-6,6a, 7,8,9,10,10a,11-octahydro-11-naphthacenone.

17. The process of claim **4**, wherein the said 9beta-acetyloctahydro-11-naphthacenone is oxidized to 6-desoxy-6-nitrodaunomycinone with thallium trinitrate or cerium ammonium nitrate or iodobenzenediacetate using with each oxidant a catalytic quantity of 2,3-dichloro-5,6-dicyanobenzoquinone.

18. The process of claim 4 wherein said 9beta-acetyloctahydro-11-naphthacenone is oxidized with cerium ammonium nitrate or thallium trinitrate or iodobenzene diacetate to 9beta-acetyl-7alpha,9alpha-dihydroxy-4-methoxy-6-nitro-6,6a,7,8, 9,10,10a,11-octahydro-5,11,12-naphthacenetrione.

19. The process of claim 4, wherein the alkali metal alkoxide is sodium methoxide generated from sodium hydride and a catalytic quantity of methanol in toluene.

20. The process of claim 4, wherein the aprotic solvent for condensing the acetonide with 1,4-dihydro-4,4,5-trimethoxy-1-oxonaphthalene is acetonitrile; the thus-produced 1-oxotetrahydronaphthalene is cyclized with sodium methoxide; the thus-produced decahydro-11-naphthacenone is converted to the 9beta-acetyloctahydro-11-naphthacenone with mercuric oxide in an acidic medium; the thus-produced 9beta-acetyloctahydro-11-naphthacenone is oxidized to the decahydro-5,11,12-naphthacenetrione with thallium trinitrate or cerium ammonium nitrate or iodobenzenediacetate; the thusproduced decahydro-5,11,12-naphthacenetrione is converted to a daunomycinone titanium compound by a Nef reaction, using sodium methoxide, and a thus-formed intermediate is treated with titanium trichloride.

21. A process of synthesizing methyl cis-3,5-dihydroxy-5-(trimethylsilylethynyl)cyclohex-1-ene-1-carboxylate from m-anisic acid comprising the steps of Birch reduction with lithium in ammonia to produce 5-oxocyclohex-2-ene-1-carboxylic acid, methylation of said cyclohex-2-ene-1-carboxylic acid to methyl 5-oxocyclohex-2-ene-1-carboxylate with diazomethane, trimethylsilylethynylation of said cyclohex-2-ene-1-carboxylate with cerium dichloride trimethylsilylacetylene to produce methyl cis-5-hydroxy-5-(trimethylsilylethynyl)cyclohex-2-ene-1-carboxylate, and conversion to an epoxide and opening of the resulting epoxide ring to give said cyclohex-1-ene-1-carboxylate.

22. The process of claim 21 wherein:

the reaction mixture is kept cold during esterification with diazomethane and the ethanol that is present in the esterification reaction mixture is removed by azeotropic distillation with benzene;

methyl ester is treated with cerium dichloride trimethylsilylacetylene at a low temperature to prevent formation of a lactone;

the epoxide is formed by oxidation with t-butyl hydroperoxide in the presence of molybdenum hexacarbonyl catalyst and isolating the thus-produced epoxide; and

the epoxide ring is opened with 1,8-diazabicyclo [5.4.0]-undec-7-ene or 1,5-diazabicyclo [4.3.0]non-5-ene or sodium methoxide in methanol; the latter conditions also remove the trimethysilyl group to give methyl cis 3,5-dihydroxy-5-ethynylcyclohex-1-ene-1-carboxylate.

23. A process for producing methyl 3alpha,5alpha-dihydroxy-5beta-(trimethylsilylethynyl)-2alpha-nitromethylcyclohexane-1beta-carboxylate comprising the steps of reacting methyl cis-3,5-dihydroxy-5-(trimethylsilylethynyl)cyclohex-1-ene-1-carboxylate with nitromethane in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene or 1,5-diazabicyclo[4.3.0]non-5-ene or sodium hydride in an aprotic solvent that can form hydrogen bonds with hydropyl groups.

24. A process for producing methyl 3alpha,5alpha-dihydroxy-5beta-ethynyl-2alpha-nitro-methylcyclohexane-1beta-carboxylate comprising the steps of reacting methyl cis-3,5-dihydroxy-5-beta-ethynylcyclohex-1-ene-1-carboxylate with nitromethane in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene or 1,5-diazabicyclo [4.3.0 non-5-ene or sodium hydride or potassium hydride in an aprotic solvent that can form hydrogen bonds with hydroxyl groups.

25. The process of claim 23 carried out in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene, wherein the aprotic solvent is dimethyl sulfoxide.

26. The process of claim 23 carried out in the presence of sodium hydride, wherein the aprotic solvent is dimethyl sulfoxide.

27. A process for preparing methyl 3-alpha,5-alpha-dihydroxy-5-beta-(trimethylsilylethynyl)-2alpha-nitromethylcyclohexane-1-beta-carboxylate comprising reacting methyl cis-(2,3alpha-epoxy-5alpha-hydroxy-5beta-(trimethylsilylethynyl)cyclohexane-1alpha-carboxylate with nitromethane in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene in an aprotic solvent.

28. The process of claim 27, wherein the aprotic solvent is dimethyl sulfoxide.

29. Methyl 3alpha,5alpha-dihydroxy-5beta-(trimethylsilylethynyl)-2alpha-nitromethylcyclohexane-1beta-carboxylate.

30. The 3,5-acetonide of methyl 3alpha,5alpha-dihydroxy-5beta-(trimethylsilylethynyl)-2alpha-nitromethylcyclohexane-1beta-carboxylate.

31. A process for preparing the compound of claim 30, comprising reacting 3alpha,5alpha-dihydroxy-5beta-(trimethylsilylethynyl)-2alpha-nitromethylcyclohexane-1beta-carboxylate with an acetonide-forming reagent.

32. The process of claim 31, wherein the acetonide-forming reagent is 2-methoxypropene and acetonide formation is carried out in the presence of pyridinium tosylate.

33. The process of converting 5-alkoxy-1-naphthol to a corresponding juglone alkyl ether 4-acetal, by reaction thallium trinitrate or iodobenzenediacetate in trimethyl orthoformate and the appropriate solvent to provide the ketal.

34. The process of claim 33, wherein the 5-alkoxy-1-naphthol is 5-methoxy-1-naphthol, the oxident is iodobenzenediacetate, the solvent is methanol and trimethylorthoformate and sodium bicarbonate is present, and the thus-produced juglone alkyl ether ketal is 1,4-dihydro-4,4,5-trimethoxy-1-oxonaphthalene.

35. The process of claim 24 carried out in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene, wherein the aprotic solvent is dimethyl sulfoxide.

36. The process of claim 24 carried out in the presence of sodium hydride, wherein the aprotic solvent is dimethyl sulfoxide.

37. A method according to claim 1 further comprising the steps of:

adding nitromethane to the said dihydroxyethynyl ester to give methyl 3alpha,5alpha-dihydroxy-5beta-(trimethylsilylethynyl)-2alpha-nitromethyl-hexane-1beta-carboxylate; and

forming the acetonide of methyl 3alpha,5alpha-dihydroxy-5beta-(trimethylsilylethynyl)-2alpha-nitromethylcyclohexane-1beta-carboxylate.

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