DOWNLOAD PDF CHEMISTRY OF 1,2-DITHIINS

Chapter 1 : Eric Block - Publications

1,2-Dithiins (o-dithiins, 1,2-dithia-3,5-cyclohexadienes, 1) are important compounds in the biological and chemical sciences. This review, which covers the available literature.

Furthermore these novel 1,2-dithiin containing substances have beneficial antiviral and antibacterial properties. The 1,2-dithiin class of heterocycles have been of interest due to their interesting physical and biological properties. Among these natural products is thiarubrine A, isolated from leaves of Aspilia mossambicesis and A. Planta Medica , 3, Other thiarubines which possess antifungal and antibacterial activity have been described Towers, G. These compounds are both heat and light sensitive, and easily convert to the corresponding thiophenes under proper thermal or photochemical conditions. All of the natural products possess acetylenic sidechains in the 3- and 6-positions of the dithiin, which may in part account for their instability. Additionally, compounds related to dithiins have been known to possess antiviral, antibacterial and antifungal activities Hudson, J. Plant Physiol, , No reports of the total synthesis of any naturally occurring thiarubrines have appeared in the literature, possibly due to the thermal and photochemical instability of these molecules. Furthermore, no biological data for the 3,6-disubstituted-1,2-dithiins without the acetylenes has been reported prior to the recent disclosure by the current inventors in August Truong, T. See also Abstract of W. In an effort to avoid these limitations, a series of novel symmetrical and unsymmetrical dithiins were synthesized and their antifungal properties were determined. Schroth and coworkers Schroth, W. This synthetic process involves the addition of benzyl mercaptan to a 1,4-diaryl-1,3-diacetylene, followed by reduction of the benzyl groups with sodium in ammonia and oxidation of the sulfide anions to the dithiin with iodine or potassium ferricyanide. Although this method was most useful for the preparation of 3,6-diaryl-1,2-dithiins, it is less satisfactory for the synthesis of 1,2-dithiins with substituents other than aromatic rings in the 3- and 6-positions of the dithiin. Furthermore the process is unattractive for large scale reactions since it involves the use of liquid ammonia and reactive alkali metals which may be hazardous to handle in large quantities. Citation or identification of any reference in Section 2 of this application shall not be construed as an admission that such reference is available as prior art to the present invention. Also the fragment R. The preferred protecting groups for alcoholic functions include, but are not limited to, the following: The preferred protecting groups for nitrogen include, but are not limited to, the following: The preferred protecting groups for carbonyl oxygen include, but are not limited to, the following: The preferred protecting groups for sulfur include, but are not limited to, the following: The novel process comprises reacting a thiol with a symmetrical or unsymmetrical 1,3-diyne to form a bis alkylthio butadiene; eliminating two molecules of a two-carbon fragment from the bis alkylthio butadiene to generate a bis thiyl butadiene dianion; and oxidizing the two thiyl anions to form 3,6-disubstituted-1,2 dithiin. The present invention further encompasses the novel compounds capable of being synthesized by the novel process. These compounds include but are not limited to the following dithiin compounds: Both the novel process for synthesis and the novel disubstituted dithiins are encompassed by the present invention. Also encompassed are pharmaceutical compositions containing the disubstituted dithiins for use as antifungal, antibacterial and antiviral agents. Detailed Description of the Invention The 1,2-dithiin derivatives described in this invention can be prepared by synthetic methods outlined below. The process described herein in general starts with a 1,4-disubstituted-1,3-diyne 1. The diyne is allowed to react with to mole percent of a thiol of the type 2 to give a 1,4-bis alkylthio butadiene adduct 3. The reaction temperature for this step is from 0. The 1,4-bis alkylthio butadiene adduct 3 is dissolved in an anhydrous solvent and treated with to mole percent of a basic reagent. The reaction is generally performed under a nitrogen atmosphere and at a temperature of The reaction mixture is then treated with 50 to mole percent of an oxidizing agent, usually dissolved in an aqueous solution. This step in the process is usually performed at a reaction temperature of C. A liquid-liquid extraction process and chromatographic purification provides the 3,6-disubstituted-1,2-dithiin 4. Scheme II provides two alternative embodiments of Scheme I to synthesize the 3,6-disubstituted-1,2 dithiin e. As also described in Scheme II, the appropriate 1,4-disubstituted-1,3-diyne 1 can be prepared using established synthetic methods and protecting

groups to provide desired unsymmetrical 3,6-disubstituted-1,2-dithiins of general structure 4. This is exemplified in Scheme II wherein the 1,4-disubstituted-1,3-diyne 5 is reacted with tert-butyldimethylsilyl chloride to form a protected diyne 8 ; the diyne 8 is then reacted with the mercaptan HSCH. With unsymmetrical 3,6-disubstituted-1,2-dithiins, the cyclized product 4 can be converted to other 3,6-disubstituted-1,2-dithiin derivatives using established synthetic methods and protecting groups as outlined in Schemes III to VII. These Schemes demonstrate the versatility of the dithiin product 4. The above novel synthetic method is preferably conducted in a reaction solvent selected from the group consisting of tetrahydrofuran, diethyl ether, diisopropyl ether, t-butyl methyl ether, t-butyl ethyl ether, ethylene glycol, ethylene glycol methyl ether, diethylene glycol methyl ether, dichloromethane, dichloroethane, dimethylformamide, methanol, ethanol, benzene, toluene, dimethylacetamide, dimethylsulfoxide, N-methylpyrrolidinone, water, and mixtures thereof; and where the reaction temperature for the reaction of the thiol with the diyne is The preferred basic reagent for the novel synthetic method is selected from the group consisting of sodium amide, potassium amide, lithium amide, sodium hydride, n-butyllithium, s-butyllithium, phenyllithium, triphenylmethyllithium, t-butyllithium, potassium t-butoxide, sodium t-butoxide, sodium methoxide, sodium s-butoxide, lithium diisopropylamide, sodium diisopropylamide, potassium diisopropylamide, sodium bis trimethylsilyl amide, potassium bis trimethylsilyl amide, lithium bis trimethylsilyl amide, lithium isopropylcyclohexylamide, potassium isopropylcyclohexylamide, sodium isopropylcyclohexylamide, 1,8-diazabicyclo[5. The preferred oxidizing agent for the novel synthetic method is selected from the group consisting of bromine, chlorine, iodine, osmium tetroxide, potassium permanganate, peracetic acid, trifluoroperacetic acid, m-chloroperbenzoic acid, N-bromosuccinimide, N-chlorosuccinimide, N-iodosuccinimide, sodium periodate, potassium periodate, potassium peroxymonosulfate OXONE , potassium dichromate, pyridinium chlorochromate, pyridinium dichromate, potassium ferrocyanide, potassium ferrocyanide trihydrate, potassium superoxide, hydrogen peroxide, bis trimethysilyl peroxide, lead tetraacetate, lithium perchlorate, lithium peroxide, manganese dioxide, nickel II oxide, nickel peroxide, potassium chromate, sodium nitrate, potassium nitrate, nitric acid, silver I oxide, silver II oxide, sodium percarbonate, sodium perchlorate, lithium perchlorate, sodium peroxide, tetrabutylammonium chlorochromate, tetrabutylammonium periodate and benzoyl peroxide. The pharmaceutical composition comprising the dithiin derivative or its pharmaceutically acceptable salt used for such administration may also contain pharmaceutically acceptable excipients and carriers, acceptable in the sense of compatible with other ingredients and not deleterious to the recipient thereof. In order to treat a fungal infection, the antifungal agents described in this invention may be administered to a warm-blooded animal intravenously, intraperitoneally, subcutaneously, intramuscularly, orally, topically, by aerosol, or combinations thereof. In general, the pharmaceutical compositions or formulations are prepared by uniformly and intimately bringing into association the active ingredient with a liquid carrier or finely divided solid carrier or both, and then if necessary shaping the product. Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion and as a bolus, etc. A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. Formulations suitable for topical administration include lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the ingredient to be administered in a suitable liquid carrier. Formulations suitable for topical administration to the skin may be presented as ointments, creams, gels and pastes comprising the ingredient to be administered an a pharmaceutically acceptable carrier. A preferred

topical delivery system is a transdermal patch containing the ingredient to be administered. Formulations suitable for nasal administration wherein the carrier is a solid include a coarse powder having a particle size, for example, in the range 20 to microns which is administered in the manner in which snuff is taken, i. Suitable formulations wherein the carrier is a liquid, for administration, as for example, a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient. Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze-dried lyophilized condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit, daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the administered ingredient. It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example, those suitable for oral administration may include flavoring agents. The antifungal agent of the dithiin derivatives described herein can be administered intravenously in a range of about 0. The antifungal agent of the dithiin derivatives described herein can be administered intraperitoneally in a range of about 0. The antifungal agent of the dithiin derivatives described herein can be administered orally in a range of about 1. The antifungal agent of the dithiin derivatives described herein can be administered topically including to skin, ocular and oral tissues in a range of about 1. The antifungal agent of the dithiin derivatives described herein can be administered by aerosol in a range of about 5. EXAMPLES The present invention may be more fully understood from the following examples, which are given by way of illustration and not by way of limitation. Anhydrous dimethylformamide DMF was obtained from Aldrich. Flash column chromatography was performed on Whatman mesh silica gel using nitrogen pressure. NMR shifts were expressed in ppm downfield from internal tetramethylsilane. NMR coupling constants are reported in Hertz. Melting points were determined using a Buchi model melting point apparatus and are uncorrected. After cooling the solution to room temperature, mL of cold acetone was added. The light yellow crystalline isothiouronium salt precipitated immediately and was collected by filtration after standing for 15 minutes at 5. The solid was washed with 7 L of cold acetone and twice with diethyl ether 2. The above salt was divided into g and g portions and dissolved in mL and mL of water, respectively. The mixtures were quickly cooled to room temperature with an water-ice bath, then mL of ether was added to each flask and both mixtures were stirred for 5 minutes. Each reaction mixture was washed twice by mL of diethyl ether then the aqueous layer was brought to pH 7 by the addition of 6N H. The combined ether extracts were dried MgSO. This material was vacuum distilled b. The resulting clear solution was stirred under nitrogen by room temp. After 3 minutes following the addition of the diyne, the flask became slightly warm and the reaction mixture had become orange. The reaction mixture was diluted with mL of water and 50 mL of saturated sodium chloride. The solution was extracted with three mL portions of ethyl acetate and the combined organic phases were washed with mL of saturated aqueous sodium chloride. The organic phase was dried MgSO. The residue was chromatographed over silica gel ethyl acetate-hexane, 1: Example 3 3,6-Bis hydroxymethyl -1,2-Dithiin 7 To a stirred solution of the product from Example 2 1. The resulting suspension was stirred for 5 minutes then 70 mL of water was added. The reaction mixture was treated with a solution of potassium ferrocyanide 2. The reaction mixture was extracted with diethyl ether 5. The residue was chromatographed over silica gel ethyl acetatehexane, 1: Example 4 3- Acetyloxymethyl hydroxymethyl -1,2-Dithiin To a solution of The reaction mixture was stirred at 0. TLC showed a big amount of starting material. The reaction mixture was warmed to The reaction mixture was poured into a mixture of ice-cold 1M aqueous H. The organic layer was washed with saturated NaHCO.

Chapter 2 : organic chemistry - Why do dithiins have 8 Ï€-electrons? - Chemistry Stack Exchange

The ground-state geometries of 1,2-dithiete and 1,2-dithiin were optimized at both the Hartree/3-Fock and MP2 levels with the G basis set.*

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Chapter 3 : Dithiin - Wikipedia

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Chapter 4 : Author: F. Freeman

Provides a review of heterocyclic sulfur chemistry from until the present day, concluding with a study of the chemistry of 1 The Chemistry Of 1 2 Dithiins (Sulfur Reports Series) (Vol 9, Part 3): F. Freeman, N. Lozac'h, D. S. H. L. Kim, e.

SU Other References Schroth et al. Synthesis of 1,2-Dithin and 3,6-Disubstituted. Attorney, Agent or Firm: Government has certain rights in the invention. A 1,4-disulfurated-1,3-butadiene of formula: STR15 wherein R is chosen from the group consisting of benzyl, p-methoxybenzyl, 2,6-dimethoxybenzyl, diphenylmethyl, triphenylmethyl, t-butyl, 2- trimethylsilyl ethyl and acetyl; R. A 1,4-disulfurated-1,3-butadiene according to claim 1 wherein R. Thiarubrines are notable as a class of light-sensitive, biologically potent, structurally unique polyacetylenic plant pigments containing an antiaromatic 8. First identified in in species of Compositae Asteraceae used for skin infections and intestinal parasites by native people in Africa and Canada, thiarubrines show good light-mediated activity against human immunodeficiency virus HIV-1 and possess significant antibiotic, antiviral and nematicidal activity both in the light and in the dark. Ten 3,6-disubstituted 1,2-dithiins have so far been identified in nature, including some with epoxide, alcohol, or chloro groups, as well as a 1,2-dithiin 1-oxide. STR1 In addition a monosubstituted at ring position 3 1,2-dithiin has also been identified from a North African medicinal plant. Two groups have reported syntheses of simple 1,2-dithiins that could be considered models for thiarubrines, but in the 30 years since their discovery, no chemical syntheses of the natural products have been reported. The absence of a flexible chemical synthesis hampers detailed study of the biological activity and chemical and physical properties of thiarubrines. There is therefore a need for a chemical synthesis of 1,2-dithiins that allows wide flexibility in the substituents at positions 3 and 6. This route creates the S--S bond of the dithiin following elaboration of the residues that will become the substituents at positions 3 and 6 of the ultimate 1,2-dithiin, thereby minimizing the synthetic disadvantages that arise from the instability and reactivity of the 1,2-dithiin ring system. In one aspect the invention relates to a method for preparing an unsymmetrically substituted 1,4-disulfurated-1,3-butadiene comprising the sequential steps of: By the term "disulfurated" is meant that the butadiene or butadiyne contains two sulfur-containing substituents attached to the butadiene or -yne through the sulfurs. The bonding in such compounds would include them in the class of thioethers. For example, compounds of formula: STR2 wherein R is any group suitable for protecting a thiol and R. A generic depiction of the process of the first aspect of the invention would be: STR3 In this, as in all subsequent schemes containing structural formulae, the substituent groups are defined when introduced and retain that definition throughout the specification and claims. The term "alkyl" as used herein refers to linear, branched or cyclic saturated hydrocarbons of ten or fewer carbons. In a preferred method a 1,4-disulfurated-1,3-butadiyne is reacted with a triaryl or trialkylstannane in the presence of a catalyst chosen from the group consisting of palladium complexes, trialkylboron compounds and combinations of the two. The 1,4-disulfurated-1,3-butadiyne may be 1,4-bis benzylthio -1,3-butadiyne. In a preferred embodiment the triaryl or trialkylstannane is triphenyltin hydride, the catalyst is a combination of tetrakis triphenylphosphine palladium 0 plus triethyl boron, and the 1,4-disulfuratedhalostannyl-1,3-butadiene is 1,4-bis benzylthio iodo triphenylstannyl -1,3-butadiene. The method above may be further extended to include the additional step of treating the 1,4-disulfuratedhalostannyl-1,3-butadiene with a copper-palladium complex or copper complex of a first substituent residue whereby a 1,4-disulfuratedstannyl-1,3-butadiene having the substituent residue at position 1 is formed. A generic description of the process including the additional step would be: STR4 In this manner one can prepare compounds of formula: STR5 wherein R is any group suitable for protecting a thiol; R. In one embodiment R. In another embodiment R is benzyl, R. The copper-palladium complex may be derived from a terminal acetylene, copper iodide and bis triphenylphosphine palladium II chloride. The method described above can further include the additional steps of a treating the 1,4-disulfuratedstannyl-1,3-butadiene having a first substituent residue at position 1 with iodine, bromine or chlorine to produce a 1,4-disulfuratedhalosubstituted-1,3-butadiene; and b treating the resulting 1,4-disulfuratedhalosubstituted-1,3-butadiene with a copper-palladium complex or a copper complex of a second substituent residue whereby a 1,4-disulfurated-1,3-butadiene having first and second substituent

residues at positions 1 and 4, respectively, is formed. By this method one can make compounds of formula: A generic representation of the overall process, including the additional steps, would be: STR7 The method described above can be modified so as to produce symmetrically substituted 1,4-disulfurated-1,3-butadienes by carrying out the sequential steps of: By this method one can prepare symmetrically substituted compounds of formula: STR8 The method may include the additional step of treating the 1,4-disulfurated-1,4-dihalo-1,3-butadiene with a copper-palladium complex or a copper complex of a substituent residue whereby a 1,4-disulfurated-1,3-butadiene having the same substituent residue at positions 1 and 4 is formed. STR9 can arise from this method. In another aspect the invention relates to a method for synthesizing a 3,6-disubstituted 1,2-dithiin comprising the sequential steps of: The method can be illustrated schematically as shown: STR10 In one embodiment the first substituent residue R. In another embodiment the second substituent residue R. If desired, the 1,4-dimercapto-1,3-butadiene can be trapped with acetyl chloride or acetic anhydride and the resulting thioester can be hydrolyzed with an alkali metal hydroxide. This optional trapping of the dimercaptan as a bis thioester introduces extra steps, but may be of utility in some cases by allowing an extra opportunity for purification. In another aspect, the invention relates to 1,4-disulfurated-1,3-butadienes of formula: Preferred embodiments of the foregoing genus include: A particularly preferred compound from this latter group is 1,4-bis benzylthio iodo triphenylstannyl -1,3-butadiene. Other embodiments include 1,4-disulfurated-1,3-butadienes wherein R. In another aspect, the invention relates to a method as described above wherein, instead of reacting the 1,4-disulfuratedstannyl-1,3-butadiene having a first substituent residue at position 1 with iodine, bromine or chlorine to produce a 1,4-disulfuratedhalosubstituted-1,3-butadiene, one treats the 1,4-disulfuratedstannyl-1,3-butadiene having a first substituent residue at position 1 with an organolithium compound to provide a 1,4-disulfuratedlithio-1,3-butadiene having a first substituent residue at position 1. To produce monosubstituted 1,2-dithiins one can then quench the 1,4-disulfuratedlithio-1,3-butadiene with a proton source such as ammonium chloride to provide a 1,4-disulfurated-1,3-butadiene having a single substituent residue at position 1. One could also replace the lithium by a substituent using chemistry well known in the art. Alternatively one may treat the 1,4-disulfuratedstannyl-1,3-butadiene having a first substituent residue at position 1 with iodine to produce a 1,4-disulfuratediodosubstituted-1,3-butadiene; and then treat the resulting 1,4-disulfuratediodosubstituted-1,3-butadiene with an organolithium compound to provide a 1,4-disulfuratedlithio-1,3-butadiene having the substituent residue at position 1. This may also be quenched with a proton source to provide a 1,4-disulfurated-1,3-butadiene having a single substituent residue at position 1. In all of the processes that are described below, it is necessary to remember that both the regiochemistry of 1,2,4,3-addition and the Z,Z stereochemistry are essential to the subsequent success in cyclizing the disulfurated butadiene. Only one of four possible 1,4-disulfurated-1,4-disubstituted butadienes will work: If other protecting groups than benzyl are desired, the appropriate precursor can replace benzyl bromide. For the purpose of synthesizing dithiins, any of the protecting groups well-known in the art for protecting sulfur could be employed. It is only necessary that the group mask the SH functionality until the substituents adjacent the sulfurs have been elaborated, and then be capable of being removed to provide free mercapto groups SH without destroying the substituents. Thus, for example, p-methoxybenzyl, 2,6-dimethoxybenzyl, diphenylmethyl, triphenylmethyl, 2- trimethylsilyl ethyl or t-butyl could be used in place of the benzyl protecting group. The processes of the invention are illustrated and exemplified as shown: STR13 Treatment of the appropriately protected 1,4-sulfurated-1,3-butadiyne, in this case the benzyl-protected 3, with 2 equivalents of Ph. The triphenyltin hydride could be replaced with other tin hydrides, such as trimethyltin hydride or tributyltin hydride, but the product of the triphenyltin hydride addition is nicely crystalline and provides, in this case, a distinct advantage in purification. The hydrostannylation of acetylenes is known to be promoted by free radical initiators such as AIBN, as well as by trialkylborons and palladium complexes, and we have found that a mixture of palladium complex and triethylboron is particularly effective at maximizing the yield and minimizing the dimerization of the tin species, while still allowing 1,2,4,3 addition and production of butadienes with pure 1,4- Z,Z -sulfur substitution. The formation of 4 from 3 would not have been predicted because alkyl- or trimethylsilyl-substituted 1,3-diynes are reported to undergo only

monohydrostannation, and then with tin attaching itself to the 2 or 4 position rather than the 1 or 3 position. Surprisingly, regio-differentiation is simply achieved by iododestannylation of 4 with 1. Iodine was used to prepare the vinyl halide because it is easy to handle and provides a good leaving group, but, although iodine is preferred, there appears no reason that bromine or chlorine would not also function in the reaction. Interestingly, the addition of the first halogen iodine appears to deactivate the other double bond of the butadiene to replacement of the tin. Thus, conversion of 5 or 4 to E,E -1,4-bis benzylthio -1,4-diiodo-1,3-butadiene 6 was slower, requiring overnight stirring. The polyyne side chains are introduced by a series of Pd II -mediated coupling reactions which occur smoothly even in the case of 5, which contains both triphenylstannyl and iodo groups: In the example shown, a Cu-Pd complex of an acetylene was used to displace the iodo substituent because the target is an acetylene-substituted 1,2-dithiin thiorubrin B. If, however, one wished to synthesize an alkene or alkane-substituted 1,2-dithiin, one could use a copper-palladium complex of an alkene or an alkyl cuprate, respectively. Because it may be of interest to introduce polar functionality into thiarubrine analogs, one could employ palladium or copper species containing ethers, esters, amides and similar functionalities, which could then be cleaved by well-known procedures to alcohols, carboxylic acids and amines, respectively, if desired. Moreover, because of the acidity of the acetylenic proton in 10 below , one can introduce all manner of polar substituents that will ultimately be attached to the 1,2-dithiin through the acetylene. In addition, the lithiation chemistry described below allows wide latitude in the substituents that can be attached directly to the 1,2-dithiin ring via incorporation into the precursor. Brief treatment of 7 with iodine in methylene chloride provides E,Z -1,4-bis benzylthio iodo trimethylsilyl hexa-1,3-dieneyne 8. As before, other halogens bromine and chlorine could be employed in place of iodine, but iodine is preferred because it is more convenient to work with and easier to displace. The ease of the reaction with iodine, once the triphenyltin has been replaced by the acetylenic residue, indicates that there is some apparent deactivation of the tin towards halogen replacement that arises from the presence of the first halogen on the C-4 carbon. One might hypothesize that this may be attributed to an electronic effect through conjugation, but applicants do not wish to be held to that speculative mechanism. Reaction of 8 with 1,3-pentadiyne gave Z,Z -3,6-bis benzylthio trimethylsilyl undeca-3,5-diene-1,7,9-triyne 9 which, upon desilylation with TBAF, afforded Z,Z -3,6-bis benzylthio undeca- 3,5-diene-1,7,9-triyne Reaction of this compound with vinyl bromide and CuI Ph. When symmetrically disubstituted butadienes are desired e. Thus coupling of diiodo compound 6 with trimethylsilylethyne affords symmetrical Z,Z -1,8-bis trimethylsilyl -3,6-bis benzylthio octa-3,5-diene-1,7-diyne When the sulfur-protecting group is benzyl, deprotection may prove difficult due to the high reactivity of the polyyne functionalities. In this case, other protecting groups can be considered, or particular conditions for the selective removal of the benzyl can be devised. In the examples below, the latter course was chosen. As an alternative to the process described above, one can react the distannyl compound 4 or the iodobutadiene 5 or 8 with an alkylithium and generate a vinylithium species in which the lithium can be replaced by a wide variety of electrophilic species by procedures well known in the art for reactions of vinylithium reagents. By this means one could introduce, for example, a carboxylate via ClCOOEt , an aldehyde via DMF addition , an alcohol via aldehyde addition , or even a hydroxy-ether via ethylene oxide addition , all directly attached to the ultimate 1,2-dithiin. A solution of Z methoxybutenyne 20 g, 2. A solution of n-BuLi 2. After stirring at The mixture was cooled to The suspension turned into a dark brown solution upon warming to The resulting solution was stirred at room temperature overnight. Ether 35 mL and water 20 mL were added, the ether layer was separated, and the aqueous layer was extracted by ether 2. The combined organic layers were washed with NH. The crude oil was purified by flash column chromatography 1: A pale yellow solid 3 was obtained 0.

Chapter 5 : Masato Koreeda - Publications

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Furthermore these novel 1,2-dithiin containing substances have beneficial antiviral and antibacterial properties. The 1,2-dithiin class of heterocycles have been of interest due to their interesting physical and biological properties. Among these natural products is thiarubrine A, isolated from leaves of Aspilia mossambicesis and A. Planta Medica , 3, Other thiarubines which possess antifungal and antibacterial activity have been described Towers, G. These compounds are both heat and light sensitive, and easily convert to the corresponding thiophenes under proper thermal or photochemical conditions. All of the natural products possess acetylenic sidechains in the 3- and 6-positions of the dithiin, which may in part account for their instability. Additionally, compounds related to dithiins have been known to possess antiviral, antibacterial and antifungal activities Hudson, J. Plant Physiol, , No reports of the total synthesis of any naturally occurring thiarubrines have appeared in the literature, possibly due to the thermal and photochemical instability of these molecules. Furthermore, no biological data for the 3,6-disubstituted-1,2-dithiins without the acetylenes has been reported prior to the recent disclosure by the current inventors in August Truong, T. See also Abstract of W. In an effort to avoid these limitations, a series of novel symmetrical and unsymmetrical dithiins were synthesized and their antifungal properties were determined. Schroth and coworkers Schroth, W. This synthetic process involves the addition of benzyl mercaptan to a 1,4-diaryl-1,3-diacetylene, followed by reduction of the benzyl groups with sodium in ammonia and oxidation of the sulfide anions to the dithiin with iodine or potassium ferricyanide. Although this method was most useful for the preparation of 3,6-diaryl-1,2-dithiins, it is less satisfactory for the synthesis of 1,2-dithiins with substituents other than aromatic rings in the 3- and 6-positions of the dithiin. Furthermore the process is unattractive for large scale reactions since it involves the use of liquid ammonia and reactive alkali metals which may be hazardous to handle in large quantities. Citation or identification of any reference in Section 2 of this application shall not be construed as an admission that such reference is available as prior art to the present invention. G1 and G2 can be an alkyl or branched alkyl radical comprising 1 to 10 carbon atoms, or a cycloalkyl radical comprising 3 to 10 carbon atoms; R1 and R4 are independent of each other and not necessarily equal to each other, but in some instances can be equal to each other. R5 can also be an aryl radical of the type STR7 where R14, R15 and R16 are as defined above; R6 can be the same as or different from R5 and is defined as hydrogen, an alkyl or branched alkyl radical comprising 1 to 10 carbon atoms, a cycloalkyl radical of 3 to 10 carbon atoms, a protecting group as described in Greene et al. R11 and R12 can be the same or different or be part of a ring comprising 2 to 10 carbon atoms; R11 can be hydrogen, an alkyl or branched alkyl radical comprising 1 to 10 carbon atoms, a cycloalkyl radical of 3 to 10 carbon atoms, or a protecting group as described in Greene et al. The preferred protecting groups for alcoholic functions include, but are not limited to, the following: The preferred protecting groups for nitrogen include, but are not limited to, the following: The preferred protecting groups for carbonyl oxygen include, but are not limited to, the following: The preferred protecting groups for sulfur include, but are not limited to, the following: The novel process comprises reacting a thiol with a symmetrical or unsymmetrical 1,3-diyne to form a bis alkylthio butadiene; eliminating two molecules of a two-carbon fragment from the bis alkylthio butadiene to generate a bis thiyl butadiene dianion; and oxidizing the two thiyl anions to form 3,6-disubstituted-1,2 dithiin. The present invention further encompasses the novel compounds capable of being synthesized by the novel process. These compounds include but are not limited to the following dithiin compounds: Both the novel process for synthesis and the novel disubstituted dithiins are encompassed by the present invention. Also encompassed are pharmaceutical compositions containing the disubstituted dithiins for use as antifungal, antibacterial and antiviral agents. Detailed Description of the Invention The 1,2-dithiin derivatives described in this invention can be prepared by synthetic methods outlined below. The process described herein in general starts with a 1,4-disubstituted-1,3-diyne 1. The diyne

is allowed to react with to mole percent of a thiol of the type 2 to give a 1,4-bis alkylthio butadiene adduct 3. The 1,4-bis alkylthio butadiene adduct 3 is dissolved in an anhydrous solvent and treated with to mole percent of a basic reagent. The reaction mixture is then treated with 50 to mole percent of an oxidizing agent, usually dissolved in an aqueous solution. This step in the process is usually performed at a reaction temperature of C. A liquid-liquid extraction process and chromatographic purification provides the 3,6-disubstituted-1,2-dithiin 4. Scheme II provides two alternative embodiments of Scheme I to synthesize the 3,6-disubstituted-1,2 dithiin e. As also described in Scheme II, the appropriate 1,4-disubstituted-1,3-diyne 1 can be prepared using established synthetic methods and protecting groups to provide desired unsymmetrical 3,6-disubstituted-1,2-dithiins of general structure 4. With unsymmetrical 3,6-disubstituted-1,2-dithiins, the cyclized product 4 can be converted to other 3,6-disubstituted-1,2-dithiin derivatives using established synthetic methods and protecting groups as outlined in Schemes III to VII. These Schemes demonstrate the versatility of the dithiin product 4. The preferred basic reagent for the novel synthetic method is selected from the group consisting of sodium amide, potassium amide, lithium amide, sodium hydride, n-butyllithium, s-butyllithium, phenyllithium, triphenylmethyllithium, t-butyllithium, potassium t-butoxide, sodium t-butoxide, sodium methoxide, sodium s-butoxide, lithium diisopropylamide, sodium diisopropylamide, potassium diisopropylamide, sodium bis trimethylsilyl amide, potassium bis trimethylsilyl amide, lithium bis trimethylsilyl amide, lithium isopropylcyclohexylamide, potassium isopropylcyclohexylamide, sodium isopropylcyclohexylamide, 1,8-diazabicyclo[5. The preferred oxidizing agent for the novel synthetic method is selected from the group consisting of bromine, chlorine, iodine, osmium tetroxide, potassium permanganate, peracetic acid, trifluoroperacetic acid, m-chloroperbenzoic acid, N-bromosuccinimide, N-chlorosuccinimide, N-iodosuccinimide, sodium periodate, potassium periodate, potassium peroxymonosulfate OXONE , potassium dichromate, pyridinium chlorochromate, pyridinium dichromate, potassium ferrocyanide, potassium ferrocyanide trihydrate, potassium superoxide, hydrogen peroxide, bis trimethysilyl peroxide, lead tetraacetate, lithium perchlorate, lithium peroxide, manganese dioxide, nickel II oxide, nickel peroxide, potassium chromate, sodium nitrate, potassium nitrate, nitric acid, silver I oxide, silver II oxide, sodium percarbonate, sodium perchlorate, lithium perchlorate, sodium peroxide, tetrabutylammonium chlorochromate, tetrabutylammonium periodate and benzoyl peroxide. The pharmaceutical composition comprising the dithiin derivative or its pharmaceutically acceptable salt used for such administration may also contain pharmaceutically acceptable excipients and carriers, acceptable in the sense of compatible with other ingredients and not deleterious to the recipient thereof. In order to treat a fungal infection, the antifungal agents described in this invention may be administered to a warm-blooded animal intravenously, intraperitoneally, subcutaneously, intramuscularly, orally, topically, by aerosol, or combinations thereof. In general, the pharmaceutical compositions or formulations are prepared by uniformly and intimately bringing into association the active ingredient with a liquid carrier or finely divided solid carrier or both, and then if necessary shaping the product. Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion and as a bolus, etc. A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. Formulations suitable for topical administration include lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the ingredient to be administered in a suitable liquid carrier. Formulations suitable for topical administration to the skin may be presented as ointments, creams, gels and pastes comprising the ingredient to be administered an a pharmaceutically acceptable carrier. A preferred

topical delivery system is a transdermal patch containing the ingredient to be administered. Formulations suitable for nasal administration wherein the carrier is a solid include a coarse powder having a particle size, for example, in the range 20 to microns which is administered in the manner in which snuff is taken, i. Suitable formulations wherein the carrier is a liquid, for administration, as for example, a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient. Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze-dried lyophilized condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit, daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the administered ingredient. It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example, those suitable for oral administration may include flavoring agents. The antifungal agent of the dithiin derivatives described herein can be administered intravenously in a range of about 0. The antifungal agent of the dithiin derivatives described herein can be administered intraperitoneally in a range of about 0. The antifungal agent of the dithiin derivatives described herein can be administered orally in a range of about 1. The antifungal agent of the dithiin derivatives described herein can be administered topically including to skin, ocular and oral tissues in a range of about 1. The antifungal agent of the dithiin derivatives described herein can be administered by aerosol in a range of about 5. EXAMPLES The present invention may be more fully understood from the following examples, which are given by way of illustration and not by way of limitation. Anhydrous dimethylformamide DMF was obtained from Aldrich. Flash column chromatography was performed on Whatman mesh silica gel using nitrogen pressure. NMR shifts were expressed in ppm downfield from internal tetramethylsilane. NMR coupling constants are reported in Hertz. Melting points were determined using a Buchi model melting point apparatus and are uncorrected. After cooling the solution to room temperature, mL of cold acetone was added. The above salt was divided into g and g portions and dissolved in mL and mL of water, respectively. The mixtures were quickly cooled to room temperature with an water-ice bath, then mL of ether was added to each flask and both mixtures were stirred for 5 minutes. This material was vacuum distilled b. The resulting clear solution was stirred under nitrogen by room temp. After 3 minutes following the addition of the diyne, the flask became slightly warm and the reaction mixture had become orange. The reaction mixture was diluted with mL of water and 50 mL of saturated sodium chloride. The solution was extracted with three mL portions of ethyl acetate and the combined organic phases were washed with mL of saturated aqueous sodium chloride. The organic phase was dried MgSO4 and concentrated in vacuo. The residue was chromatographed over silica gel ethyl acetate-hexane, 1: Example 3 3,6-Bis hydroxymethyl -1,2-Dithiin 7 To a stirred solution of the product from Example 2 1. The resulting suspension was stirred for 5 minutes then 70 mL of water was added. The reaction mixture was treated with a solution of potassium ferrocyanide 2. The residue was chromatographed over silica gel ethyl acetatehexane, 1: TLC showed a big amount of starting material. Example 5 3,6-Bis[cyclopropylcarbonyloxy methyl]-1,2-Dithiin and 3-[cyclopropylcarbonyloxy methyl]hydroxymethyl-1,2-Dithiin To a stirred solution of 2. The reaction mixture was allowed to warm up to room temperature overnight then it was poured into a vigorously stirred, cold mixture of mL of diethyl ether and 50 mL of 1M aqueous phosphoric acid. The organic phase was dried MgSO4 and concentrated in vacuo to give 2. This product was purified by chromatography over g of silica gel ethyl acetate-hexane, 1: Continued elution afforded 1. Next, dithiin diol 30 mg; 0. The organic phase was dried Na2 SO4 and concentrated in vacuo. The crude material was chromatographed on silica gel ethyl acetate-hexane, 1: Example 7 3,6-Bis[4-pyridylcarbonyloxy methyl]-1,2-Dithiin To a heterogeneous mixture of isonicotinoyl chloride hydrochloride

mg, 1. After 8 hours, the reaction was complete by thin-layer chromatography. The organic phase was concentrated in vacuo and the residue was purified by chromatography on silica gel ethyl ether to give 27 mg Example 8 3-[4-pyridylcarbonyloxy methyl]hydroxymethyl-1,2-Dithiin To a solution of isonicotinoyl chloride hydrochloride mg; 1.

Chapter 6 : 1,2-dithiin antiinfective agents - Shaman Pharmaceuticals, Inc.

Abstract This report describes the bioactivity, the chemistry, and the synthesis of 1,2-dithiins, (o-dithiin, 1,2-dithia-3,5-cyclohexadiene) and its derivatives.

Animals in groups of five each were lightly anesthetized, then the test substance, previously dissolved in aquaphor, was applied in the amount of 10 mg topically to the dorsal aspect of the right ear. Aquaphor without test substance was applied to the left ear as a control. Animals were inspected daily for five days for signs of dermal irritation and erythema, which was scored subjectively on a scale from 1 to 15, with 15 indicating severe toxicity. ICR mice, in groups of five or six each were injected with solutions of the test compound given intraperitoneally for three consecutive days for thiarubrine A and five consecutive days for the 1,2-dithiin. Animals were weighed daily and observed for mortalities over a 14 day period. An LD50 of 0. As can be seen, the results indicate that the previously unknown 1,2-dithiin compounds have good in vitro activity, with results for the more active members of the series similar to those obtained with thiarubrine A. The results indicate potent antifungal activity of the new non-acetylenic 1,2-dithiin compounds against a broad spectrum of medically important fungi. Results from the dermal irritation test see Table 2 showed that by day 5, acetylene-containing thiarubrine A elicited pronounced toxicity, with an average score of 9 for the treated ear and a normal reading of 4 for the control ear for the five animals. In contrast, the mice treated with the 1,2-dithiin lacking acetylene side chains 3,6-bis hydroxymethyl -1,2-dithiin exhibited no signs of dermal irritation or erythema over the five-day period. Results from the systemic toxicological study showed thiarubrine A to be highly toxic, with an LD50 dose of approximately 0. Overall, the results indicate that the 1,2-dithiin class of compounds has a potent antifungal profile without the adverse toxicological properties of the acetylene-containing thiarubrines. This substantiates that the acetylene moieties found within the thiarubrine class are responsible for much of the observed thiarubrines toxicity. Also, the acetylenic moieties are only partly responsible for the antiinfective properties with the 1,2-dithiin ring being the important pharmacophore for antiinfective activity. To this mixture was added 2. After stirring at rt for 20 min, 1. The reaction mixture was then stirred at rt for 3 h and was then poured into mL of water. To this liquid ammonia were added at that temperature, first 42 mg 4 equiv of lithium and then mg of diol II in 4 mL of dry THF. Soon after the completion of the additions of the diol solution, the blue color of the solution disappeared and the mixture became a white suspension. An additional amount of lithium was added in order to maintain the blue color of the mixture. The reaction mixture was allowed to gradually warm up to rt, during which time the ammonia was removed by evaporation to afford a yellow solution. The remaining ammonia was removed by rotary evaporation. The mixture was then allowed to warm up to rt and the deep-red ether and the orange aqueous layers were separated. Calcd for C6 H8 O2 S2: After stirring overnight in the dark the mixture was diluted with diethyl ether mL and partition between diethyl ether 50 mL and 3. The diethyl ether layer was washed with 3. The resulting oily residue was purified by silica gel flash column chromatography using 1: After stirring in the dark at room temperature overnight the mixture was diluted with diethyl ether 10 mL and partitioned between 3. To this solidified mixture was added 1. After stirring in the dark at room temperature overnight the mixture was diluted with diethyl ether 20 mL and partitioned between 3. After stirring in the dark at room temperature overnight the mixture was diluted with ether 20 mL and partitioned between 1. After stirring at room temperature overnight, the solution was diluted with methylene chloride 30 mL and the resulting mixture was washed first with water 20 mL and then with brine 20 mL. After stirring at that temperature for 40 min. Calcd for C6 H4 S2 O2: STR14 The invention described and claimed herein is not to be limited in scope by the specific embodiments herein disclosed, since these embodiments are intended as illustrations of several aspects of the invention. Any equivalent embodiments are intended to be within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. All references cited in the present application are incorporated by reference in their entirety.

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An efficient, generally applicable method for the synthesis of a variety of 3,6-disubstituted 1,2-dithiins has been established. The method involves the regio- and stereoselective 1,4-bis-addition.