Chemistry of 1,2-Dithiins. Synthesis of the Potent Antibiotic Thiarubrine A

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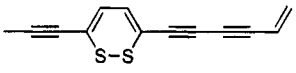
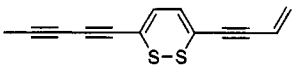
Increasing attention has recently been given to a new class of sulfur-containing heterocyclic compounds, 1,2-dithiins (1,2-dithia-3,5-cyclohexadienes), due to their unique structure and a wide range of biological activity.[1] Since the first isolations of 1,2-dithiin compounds from the roots of *Eriophyllum caespitosum* Dougl.[2,3] and *Ambrosia eliator* L.[3] by Mortensen in 1964[2] and Bohlmann in 1965,[3] nearly a dozen 1,2-dithiins have been isolated from a number of taxa of the Asteraceae.[4] It is of interest to note that some skepticism was expressed, as late as 1987, regarding the structures of these naturally occurring antiaromatic compounds.[5] The leaves of *Aspilia africana* are used in some parts of Africa to treat several diseases such as skin infection and abdominal pain.[6] Interestingly, it was also observed that wild chimpanzees selectively pick and swallow the leaves of some of these trees without chewing, thus implicating the notion that these animals consume the leaves for some special pharmacological effects rather than as their dietary source.[7] Thiarubrine A (**1**) [3-(5-hexene-1,3-diynyl)-6-(1-propynyl)-1,2-dithiin], a major leaf phytochemical of these trees, has been shown to exhibit a wide spectrum of potent antiviral, antifungal, and antibacterial activities.[8] For example,



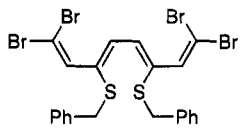
thiarubrine A (**1**)



thiarubrine B (**2**)

thiarubrine A is reported to be as effective as fungizone at a concentration of 1 ppm against *Candida albicans*.[8a] The important biological activities and unique structures of 1,2-dithiins have drawn considerable interest among synthetic[9] and theoretical chemists[10] in recent years. In the following, we describe the first total synthesis of the highly labile thiarubrine A, which features the use of the 2-(trimethylsilyl)ethyl group as a versatile thiol-protecting group.

We had earlier established, through a modification of Schroth's original method,[11] a convenient, general method for the synthesis of a variety of 3,6-disubstituted 1,2-dithiins (Scheme 1).[12] However, adaptation of this approach in the synthesis of thiarubrine A was deemed problematic since the presence of the acetylene group in the molecule might be a source of difficulty due to its competing reduction during the thiol deprotection step with metal in liquid ammonia. In this context, the three acetylene-carrying dienes **6**−**8** have been prepared from the dialdehyde (**3**; R = CHO) by the method of Corey and Fuchs.[13] Treatment of the dilithio acetylide species generated from tetrabromide **5**, obtainable from the dialdehyde **3** (R = CHO), with excess H_2O, MeI, and TMSCl produced **6** (58% from the dialdehyde), **7** (73%), and **8** (80%), respectively.



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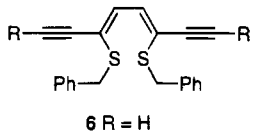

6 R = H
7 R = Me
8 R = TMS

Although the application of the above-mentioned protocol developed for the synthesis of the 1,2-dithiin ring to **6** resulted in the formation of the dithiin **4** (R = C≡CH), this diacetylenic 1,2-dithiin product (30%) was accompanied by its over-reduced diethyl analog **4** (R = Et; 10%). Moreover, subjection of the other two diacetylenic compounds **7** and **8** to similar conditions did not result in the formation of 1,2-dithiin compounds; instead, mostly reduction of the acetylenic groups took place. Subsequent exploration for an alternate approach for the synthesis of 1,2-dithiins employing a thiol-protecting group that does not require the dissolving metal/liquid ammonia conditions for its deprotection has culminated in the use of the 2-(trimethylsilyl)-ethyl group as the versatile thiol-protecting group[14] as demonstrated in the total synthesis of thiarubrine A (Scheme 2).

Another crucial issue that needed to be addressed in the synthesis of thiarubrine A concerned a method for the efficient installment of the two unsymmetric substituents at C-3 and C-6 of the 1,2-dithiin heterocycle. In this context, it appeared quite appealing to introduce dissymmetry at a relatively later stage in synthesis possibly by means of one-pot, selective, differential extension of the side chains, thus greatly reducing the overall number of synthetic steps. This strategy was subsequently put to the test using the dilithio-acetylide species generated from tetrabromide **12**. The requisite tetrabromide was obtained from commercially available 2,4-hexadiyne-1,6-diol (**9**)[15] in three steps in 63% overall yield. Thus, treatment of this diyne with the protected thiol equivalent 2-(trimethylsilyl)ethanethiol[16] in the presence of a catalytic amount of KOH in DMF at room temperature resulted in the facile regio- and stereoselective

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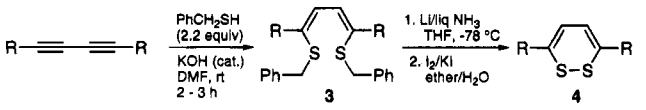
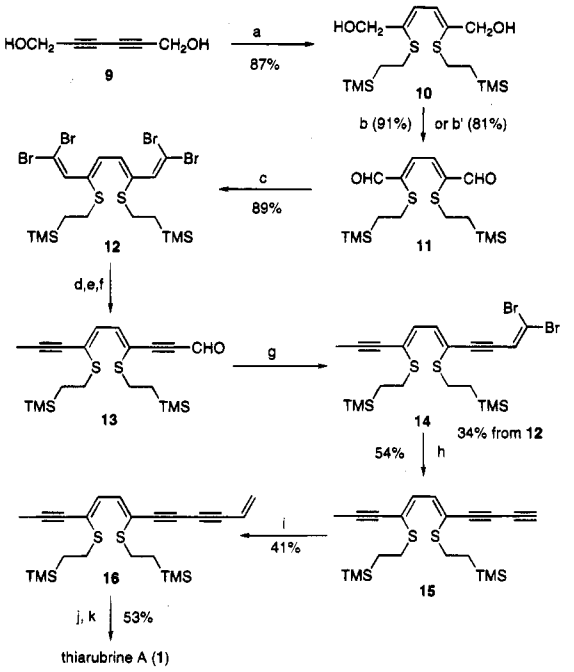
Scheme 1



Scheme 2[a]



[a] Reagents and conditions: (a) $TMSCH_2CH_2SH$ (2.2 equiv)/(KOH (cat.)/DMF, room temperature, 2 h; (b) Dess–Martin periodinane (2.1 equiv)/CH_2Cl_2, room temperature, 30 min; (b') $(COCl)_2$ (2.2 equiv)/DMSO (4.4 equiv), then NEt_3 (10 equiv)/CH_2Cl_2, −78 °C to room temperature, 5 h; (c) PPh_3 (8.0 equiv), CBr_4 (4.0 equiv)/CH_2Cl_2, 0 °C, 30 min; (d) *n*-BuLi (4.0 equiv)/THF, −78 °C, 1 h, then warmed to room temperature, 1 h; (e) MeI (1.0 equiv), −78 °C to room temperature, 7 h; (f) DMF (1.1 equiv), $BF_3{\cdot}Et_2O$ (1.0 equiv), −78 °C, 30 min; (g) PPh_3 (4.0 equiv), CBr_4 (2.0 equiv)/CH_2Cl_2, 0 °C, 30 min; (h) *n*-BuLi (2.0 equiv)/THF, −78 °C, 1 h then warmed to room temperature, 1 h; (i) $CH_2{=}CHBr$ (large excess)/toluene, $Pd(PPh_3)_4$ (cat.), CuI (cat.), NEt_3 (10 equiv), room temperature, 4 h; (j) TBAF (8.0 equiv), 3 Å molecular sieves/THF, room temperature, 1 h; (k) I_2 (10 equiv), room temperature, 30 min.

formation of the double thiol addition product **10**.[17] Conversion of diol **10** into dialdehyde **11**, achieved with the Dess–Martin periodinane reagent[18] or under Swern oxidation conditions[19] followed by chain elongation with PPh_3/CBr_4 afforded the key intermediate tetrabromide **12**. The sequential, one-pot treatments of the dilithio acetylide generated from **12**, with 1 equiv each of MeI and $DMF/BF_3{\cdot}OEt_2$, afforded the dissymmetrically extended diacetylene aldehyde **13** as the major product. The product distribution of this reaction[20] aimed at the transformation from **12** to **13** seems to suggest that the desired methylated aldehyde was obtained primarily on the statistical basis of the initial methylation step of the dilithio species. This apparent lack of control for the selective monomethylation of the dilithio acetylide generated from tetrabromide **12** may be the manifestation of ineffective orbital overlap between the two carbanionic orbitals and the rest of the diyne–diene π-orbital systems. Since aldehyde **13** was found relatively unstable, it was treated with PPh_3/CBr_4[13] immediately without purification, producing dibromide **14** (stable indefinitely in solution when stored at around 5 °C) as a bright yellow liquid in 34% overall yield from tetrabromide **12**. Treatment of dibromide **14** with 2 equiv of *n*-BuLi afforded the extremely labile triacetylene **15** in 54% yield, which was immediately coupled with vinyl bromide in the presence of $Pd(0)/Cu(I)/NEt_3$.[21] Deprotection of the 2-(trimethylsilyl)ethyl group of the ene–triyne intermediate **16** with excess TBAF in the presence of molecular sieves in THF, followed by oxidative 1,2-dithiin ring formation with iodine,[12] provided a red-colored liquid, whose proton NMR and UV spectroscopic properties were identical with those reported for thiarubrine A (**1**), in 22% overall yield from triyne **15**.

The above-mentioned 11-step synthesis from 2,4-hexadiyne-1,6-diol (**9**) constitutes the first total synthesis of this highly intriguing antiaromatic natural product thiarubrine A. The novel use of 2-(trimethylsilyl)ethanethiol as the protected sulfur atom for the eventual construction of the 1,2-dithiin heterocycle without employment of dissolving metal/liquid ammonia conditions should find wide applications in the synthesis of natural polyacetylene-containing 1,2-dithiin compounds.

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Supplementary Material Available: Experimental details for the synthesis of thiarubrine A (**1**) from 2,4-hexadiyne-1,6-diol as well as characterization data for compounds **10**–**16** and **1** (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(17) The stereochemistry of the bis-thiol adduct **9** was ascertained through comparisons of the ^1H NMR peaks of the vinyl protons of **9** (δ 6.89) with those of **3** (δ 6.81), whose stereochemistry was established by homonuclear NOE experiments.

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(20) The proton NMR analysis of the crude product mixture from the initial methylation step of the dilithio acetylide generated from tetrabromide **11** indicated that, in addition to the desired monomethylated product (ca. 51%), both the dimethylated and protonated diacetylene compounds were present at approximately 22% each in the mixture.

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