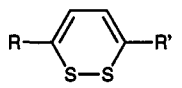
Total Synthesis of Thiarubrine B [3-(3-Buten-1-ynyl)-6-(1,3-pentadiynyl)-1,2-dithiin], the Antibiotic Principle of Giant Ragweed (*Ambrosia trifida*)

Eric Block,* Chuangxing Guo, Mohan Thiruvazhi, and Paul J. Toscano

Department of Chemistry
State University of New York at Albany
Albany, New York 12222

Received July 15, 1994

Giant ragweed (*Ambrosia trifida*), used in herbal medicine as an antiseptic and to treat intestinal worms and fever,[1] contains significant quantities (ca. 0.003% by weight) of 3-(3-buten-1-ynyl)-6-(1,3-pentadiynyl)-1,2-dithiin (thiarubrine B (**1a**)) and lesser quantities of 3-(5-hexen-1,3-diynyl)-6-(1-propynyl)-1,2-dithiin (thiarubrine A (**1b**)) and related compounds.[2] These are



1 **a**, R = CH_2=CHC≡C-, R' = MeC≡CC≡C- (thiarubine B)
b, R = CH_2=CHC≡CC≡C-, R' = MeC≡C- (thiarubine A)
c, R = R' = H

light-sensitive, deeply colored substances with a 3,6-disubstituted, 8π-electron, antiaromatic[3] 1,2-dithiin (1,2-dithia-3,5-cyclohexadiene) ring (**1**). Thiarubrines **1** were first identified in 1964–65[4,5] in species of Compositae (Asteraceae) used[6a] for skin infections and intestinal parasites by native people in Africa and Canada. Compounds **1** show good light-mediated activity against human immunodeficiency virus (HIV-1)[6b] and possess significant antibiotic, antiviral, and nematicidal activity both in the light and in the dark.[6c-g] Thus far, 10 naturally occurring, polyacetylene-derived[7ab] thiarubrines have been isolated, including some with epoxide, alcohol, or chloro substituents in the acetylenic side chains (R and R' in **1**), as well as a 1,2-dithiin 1-oxide.[2,6g-p] In spite of the fact that thiarubrines have been known for 30 years, no syntheses have been reported, hampering detailed study of biological activity and chemical and physical properties.[8] A limited number of syntheses of simple 1,2-dithiins **1** have been been reported,[9] but in most cases these approaches lack generality or give complex mixtures. We report the first total synthesis of thiarubrine B (**1a**).

A key consideration in planning syntheses of thiarubrines is the instability and reactivity of the 1,2-dithiin ring system.[9f] For this reason, we chose to defer ring generation until the final step. Formation of 3,6-disubstituted 1,2-dithiins requires that the precursors have the proper 1,4-(*Z*,*Z*) stereochemistry for the sulfur substitution pattern at the double bonds and the proper regiochemistry for the substituents. Encouraged by the report of Magriotis et al. that Bu_3SnH cleanly undergoes regio- and stereospecific addition to 1-phenylthioalkynes to give the corresponding (*E*)-1-(tributylstannyl)-1-(phenylthio)-1-alkenes,[10] we hoped that 1,4-bis(benzylthio)-1,3-butadiyne (**2**) would behave similarly, allowing direct access to a useful synthon of 3,6-disubstituted 1,2-dithiins.

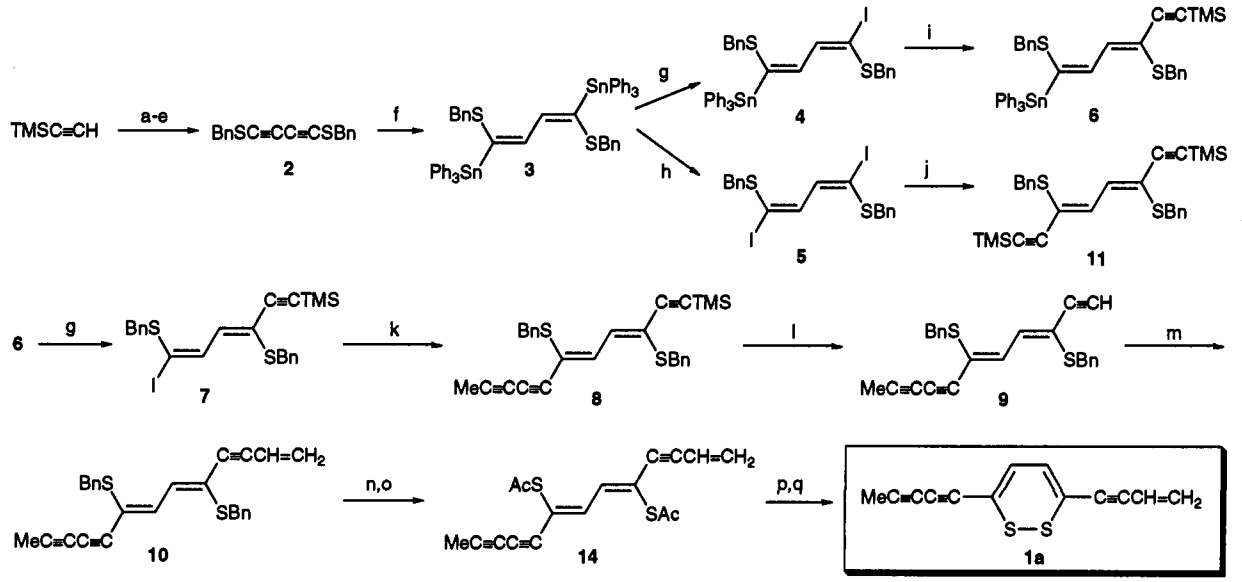
Compound **2** was readily synthesized as shown in Scheme 1. Sequential treatment of (trimethylsilyl)ethyne[11] with *n*-butyllithium, sulfur,[12] benzyl bromide, and tetra-*n*-butylammonium fluoride (TBAF) gave benzylthioethyne, and this on Glaser oxidation[13] gave **2** in 93% overall yield.[14] In the key step, treatment of **2** with 2 equiv of Ph_3SnH[15b] in the presence of $(Ph_3P)_4Pd$ and Et_3B[15d] gave crystalline (*E*,*E*)-1,4-bis(benzylthio)-1,4-bis(triphenylstannyl)-1,3-butadiene (**3**; 56% yield).[16] The stereochemical assignment for **3** was confirmed by single crystal X-ray diffraction.

Regiodifferentiation of **3** was readily achieved by replacement of one tin group with iodine,[18] giving (*E*,*E*)-1,4-bis(benzylthio)-1-iodo-4-(triphenylstannyl)-1,3-butadiene (**4**) (I_2, 1.1 equiv, 3 h, 0 °C, CH_2Cl_2; 97% yield). Replacement of the remaining tin group in **4**, or both tin groups in **3**, with iodine to give (*E*,*E*)-1,4-bis(benzylthio)-1,4-diiodo-1,3-butadiene (**5**) was slower (16 h, 25 °C; 100% yield). The polyyne side chains were introduced by a series of three Pd(II)-mediated coupling reactions, which fortunately occurred smoothly, *even in the case of 4, containing both triphenylstannyl and iodo groups*. Conversion of iodotin compound **4** into triyne-triene **10** (see Scheme 1) could be accomplished in 28% overall yield in five steps: coupling with 1

(1) Cox, D. D. *Common Flowering Plants of the Northeast*; SUNY Press: Albany, NY 1985.
(2) Lu, T.; Parodi, F. J.; Vargas, D.; Quijano, L.; Mertooetomo, E. R.; Hjortso, M. A.; Fischer, N. H. *Phytochemistry* **1993**, *33*, 113–116.
(3) (a) Cimiraglia, R.; Fabian, J.; Hess, B. A., Jr. *J. Mol. Struct. (Theochem)* **1991**, *230*, 287–293. (b) Aihara, J. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2899–2903.
(4) Mortensen, J. T.; Sørensen, J. S.; Sørensen, N. A. *Acta Chem. Scand.* **1964**, *18*, 2392–2394.
(5) (a) Bohlmann, F.; Kleine, K.-M. *Chem. Ber.* **1965**, *98*, 3081–3086. (b) Bohlmann, F.; Zdero, C. In *The Chemistry of Heterocyclic Compounds*; Gronowitz, S., Ed.; John Wiley & Sons: New York, 1985; Vol. 44, Part 1, chapter 3.
(6) (a) Rodriguez, E.; Aregullin, M.; Nishida, T.; Uehara, S.; Wrangham, R. W.; Abramowski, Z.; Finlayson, A. J.; Towers, G. H. N. *Experientia* **1985**, *41*, 419–420. (b) Hudson, J. B.; Balza, F.; Harris, L.; Towers, G. H. N. *Photochem. Photobiol.* **1993**, *57*, 675–680. (c) Towers, G. H. N.; Abramowski, Z.; Finlayson, A. J.; Zucconi, A. *Planta Med.* **1985**, 225–229. (d) Hudson, J. B.; Graham, E. A.; Fong, R.; Finlayson, A. J.; Towers, G. H. N. *Planta Med.* **1986**, 51–54. (e) Constabel, C. P.; Towers, G. H. N. *Planta Med.* **1989**, 35–37. (f) Rodriguez, E. In *Biologically Active Natural Products*; Cutler, H. G., Ed.; American Chemical Society: Washington, DC, 1988; pp 432–437. (g) Steliou, K.; Folkins, P. L.; Harpp, D. N. In *Advances in Sulfur Chemistry*; Block, E., Ed., JAI Press: Greenwich, CT, 1994; Vol. 1, pp 114–117. (h) Norton, R. A.; Finlayson, A. J.; Towers, G. H. N. *Phytochemistry* **1985**, *24*, 356–357. (i) Cosio, E. G.; Norton, R. A.; Towers, E.; Finlayson, A. J.; Rodriguez, E.; Towers, G. H. N. *J. Plant Physiol.* **1986**, *124*, 155–164. (j) Cosio, E. G.; Towers, G. H. N.; McPherson, J. *J. Plant Physiol.* **1987**, *129*, 1–11. (k) Balza, F.; Towers, G. H. N. *Phytochemistry* **1990**, *29*, 2901–2904. (l) Ellis, S.; Balza, F.; Towers, G. H. N. *Phytochemistry* **1993**, *33*, 224–226. (m) Balza, F.; Towers, G. H. N. *Methods Plant Biochem.* **1993**, *8*, 551–572. (n) A 3-substituted 1,2-dithiin may be present in *Santolina chamaecyparissus* L, a plant used in folk medicine in North Africa.[6o] (o) Lam, J.; Bildsoe, H.; Christensen, L. P.; Thomasen, T. *Acta Chem. Scand.* **1989**, *43*, 799–802. (p) Towers, G. H. N.; Bruening, R. C.; Balza, F.; Abramowski, Z. A.; Lopez-Bazzochi, I. U.S. Patent 5,202,348, April 13, 1993.
(7) (a) Gomez-Barrios, M. L.; Parodi, F. J.; Vargas, D.; Quijano, L.; Hjortso, M. A.; Flores, H. E.; Fischer, N. H. *Phytochemistry* **1992**, *31*, 2703–2707. (b) Constabel, C. P.; Towers, G. H. N. *Phytochemistry* **1989**, *28*, 93–95.
(8) All-carbon homolog of **1b**: Freeman, F.; Kim, D. S. H. L.; Rodriguez, E. *J. Org. Chem.* **1993**, *58*, 2317–2319.
(9) (a) Schroth, W.; Billig, F.; Reinhold, G. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 698–699. (b) Schroth, W.; Billig, F.; Reinhold, G. *Z. Chem.* **1965**, *5*, 352–353. (c) Schroth, W.; Billig, F.; Languth, H. *Z. Chem.* **1965**, *5*, 353–354. (d) Schroth, W.; Hintzsche, E.; Felicetti, M.; Spitzner, R.; Sieler, J.; Kempe, R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 739–741. (e) Schroth, W.; Hintzsche, E.; Viola, H.; Winkler, R.; Klose, H.; Boese, R.; Kempe, R.; Sieler, J. *Chem. Ber.* **1994**, *127*, 401–408. (f) Freeman, F.; Kim, D. S. H. L.; Rodriguez, E. *Sulfur Rep.* **1989**, *9*, 207–247. (g) Koreeda, M.; Yang, W. *Synlett* **1994**, 201–203.
(10) Magriotis, P. A.; Brown, J. T.; Scott, M. E. *Tetrahedron Lett.* **1991**, *32*, 5047–5050.
(11) Holmes, A. B.; Sporikou, C. N. *Org. Synth.* **1987**, *65*, 61–67.
(12) Harris, S. J.; Walton, D. R. M. *J. Chem. Soc., Chem. Commun.* **1976**, 1008–1009.
(13) Walton, D. R. M.; Waugh, F. *J. Organomet. Chem.* **1972**, *37*, 45–56.
(14) An alternative one-pot synthesis of **2** involves treatment of (*Z*)-1-methoxybut-1-en-3-yne with 3 equiv of *n*-BuLi,[15a] thiolation, and alkylation with benzyl bromide (52% overall yield).
(15) (a) Zweifel, G.; Rajagopalan, S. *J. Am. Chem. Soc.* **1985**, *107*, 700–701. (b) While Ph_3SnH is commercially available, it is much more economical to prepare it from Ph_3SnCl.[15c] (c) Kuivila, H. G.; Beumel, O. F., Jr. *J. Am. Chem. Soc.* **1961**, 83, 1246–1250. (d) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547–2549.
(16) Formation of **3** from **2** is particularly satisfying because *alkyl-* or *trimethylsilyl*-substituted 1,3-diynes undergo only monohydrostannation, with tin attaching itself to the 2 (or 4) position rather than the 1 (or 3) position.[17]
(17) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857–1867.
(18) Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851–3854.

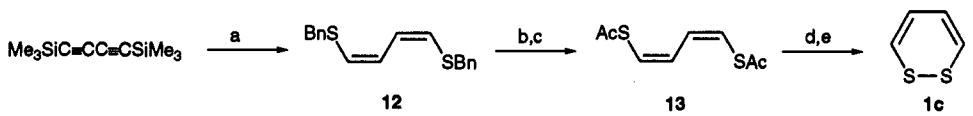
0002-7863/94/1516-9403$04.50/0

Scheme 1[a]



[a] (a) *n*-BuLi, Et_2O; (b) S_8, −78 °C; (c) BnBr; (d) *n*-Bu_4NF; (e) Cu_2Cl_2, TMEDA, O_2, Me_2CO, 93% for five steps; (f) $2Ph_3SnH$, $(Ph_3P)_4Pd$, Et_3B, toluene; −30 to 0 °C, 56%; (g) I_2, CH_2Cl_2, 0 °C, 2 h, 95–97%; (h) $2I_2$, CH_2Cl_2, 25 °C, 16 h, 100%; (i) TMSC≡CH, CuI–$(Ph_3P)_2PdCl_2$, Et_2NH, C_6H_6, 86%; (j) 3TMSC≡CH, CuI–$(Ph_3P)_2PdCl_2$, Et_2NH, C_6H_6, 73%; (k) MeC≡CC≡CH, CuI–$(Ph_3P)_2PdCl_2$, Et_2NH, C_6H_6, 57%; (l) *n*-Bu_4NF, 86%; (m) CH_2=CHBr, CuI–$(Ph_3P)_2PdCl_2$, Et_2NH, C_6H_6 70%; (n) LDMAN, THF, −80 °C, 1.5 h; (o) AcCl; (p) KOH/MeOH; (q) I_2, −30 °C, 17% for four steps.

Scheme 2[a]



[a] (a) $PhCH_2SNa$, MeOH, reflux, 48 h, 78%; (b) LDMAN, THF, −80 °C, 1.5 h; (c) AcCl, 96% for two steps; (d) KOH/MeOH; (e) I_2, −30 °C, 73% for two steps.

equiv of (trimethylsilyl)ethyne and CuI–$(Ph_3P)_2PdCl_2$ in benzene–diethylamine[19] (**4** → **6**), iododestannylation (**6** → **7**), coupling with 1,3-pentadiyne (**7** → **8**), TBAF desilylation (**8** → **9**), and coupling with vinyl bromide (**9** → **10**).[20] In addition, *double* Pd(II)-mediated coupling of diiodo compound **5** with (trimethylsilyl)ethyne afforded symmetrical **11** in 73% yield.

Due to the reactivity of the polyyne functionalities in **10**, deprotection proved to be difficult. Model studies were helpful here. Thus, as shown in Scheme 2, treatment of (*Z*,*Z*)-1,4-bis(benzylthio)-1,3-butadiene (**12**)[21] with lithium 1-(*N*,*N*-dimethylamino)naphthalenide (LDMAN)[22] followed by acetyl chloride gave (*Z*,*Z*)-1,4-bis(acetylthio)-1,3-butadiene (**13**) in 96% yield (yields of **13** were lower when **12** was cleaved with Na/NH_3[9a]). This, on sequential treatment with KOH/MeOH followed by iodine, gave 1,2-dithiin (**1c**) in 73% yield. With this precedence, we treated **10** with LDMAN in THF at −80 °C for 1.5 h and then quenched the reaction with excess acetyl chloride to give (*Z*,*Z*)-5,8-bis(thioacetyl)trideca-1,5,7-triene-3,9,11-triyne (**14**). Cleavage of **14** with methanolic KOH followed by low-temperature oxidation with iodine[23] gave thiarubrine B (**1a**) in 17% overall yield from **10**. The spectroscopic properties of **1a** (EI-MS, UV, ^1H and ^{13}C NMR) match those reported[2,6m,24] and those determined by us[25] for natural **1a**. Comparison of synthetic and natural **1a** by C_{18} HPLC (28% H_2O, 72% MeCN) with a diode array UV detector showed the compounds to be identical.[26] In addition, exposure of synthetic **1a** to light affords 3-(3-buten-1-ynyl)-5-(1,3-pentadiynyl)thiophene, identical with the light-induced monodesulfurization product of natural thiarubrine B.[26] Bioassay confirmed the identity of synthetic and natural **1a**, showing minimal inhibitory concentrations of 0.02–0.04 (synthetic) and 0.01–0.02 μg/mL (natural) toward *Candida albicans*.[26] Efforts are continuing to optimize yields, to prepare homologs of **1a** for biological testing from the now readily available **3**–**5** and **11**, and to explore the chemistry of 1,2-dithiins **1**.

Acknowledgment. We thank Professors T. Cohen, N. Fischer, F. Hauser, P. Magriotis, and N. Towers for helpful suggestions and valued assistance and X. Zhang, R. DeOrazio, and Dr. V. Eswarakrishnan for preliminary studies on this project. We gratefully acknowledge support from the National Science Foundation, the NRI Competitive Grants Program/USDA (Award No. 92-37500-8068), Sterling-Winthrop Research Institute, and McCormick and Company.

Supplementary Material Available: Experimental procedures and spectral data for **1a**–**10** and **14** and X-ray crystallographic information for **3** (17 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.

(19) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* 1975, 4467–4470. (b) Okuro, K.; Furuune, M.; Enna, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 4716–4721.

(20) Compound names: **6**, (*E*,*E*)-1,4-bis(benzylthio)-1-(triphenylstannyl)-6-(trimethylsilyl)hexa-1,3-diene-5-yne; **7**, (*E*,*Z*)-1,4-bis(benzylthio)-1-iodo-6-(trimethylsilyl)hexa-1,3-diene-5-yne; **8**, (*Z*,*Z*)-3,6-bis(benzylthio)-1-(trimethylsilyl)undeca-3,5-diene-1,7,9-triyne; **9**, (*Z*,*Z*)-3,6-bis(benzylthio)undeca-3,5-diene-1,7,9-triyne; **10**, (*Z*,*Z*)-5,8-bis(benzylthio)trideca-1,5,7-triene-3,9,11-triyne; **11**, (*Z*,*Z*)-1,8-bis(trimethylsilyl)-3,6-bis(benzylthio)octa-3,5-diene-1,7-diyne.

(21) (a) (*Z*,*Z*)-1,4-Bis(benzylthio)-1,3-butadiene (**12**) was prepared in 78% yield by refluxing $PhCH_2SNa$ with 1,4-bis(trimethylsilyl)-1,3-butadiyne in MeOH for 48 h.[21b] (b) Koreeda and Yang[9a] independently discovered a similar synthesis of **12** but provided no details.

(22) Cohen, T.; Sherbine, J. P.; Matz, J. R.; Hutchins, R. R.; McHenry, B. M.; Willey, P. R. *J. Am. Chem. Soc.* **1984**, *106*, 3245–3252

(23) Hartke, K.; Pfleging, E. *Liebigs Ann. Chem.* **1988**, 933–941.

(24) Radeglia, R.; Poleschner, H.; Schroth, W. *Z. Naturforsch.* **1988**, *43b*, 605–610.

(25) Thiarubrine B was isolated[2] by us from a sample of *Ambrosia trifida* provided by Professor N. Fischer, whom we thank.

(26) We thank Professor Towers for performing these studies.