brianthein W.[4] X-ray diffraction analysis conveniently provided a final solution to this structure problem, substantiating our hypothesis and establishing the relative stereochemistry shown in **3** and Figure 1.

Crystals of brianthein W belonged to the orthorhombic crystal class with a = 8.783 (2) Å, b = 9.486 (2) Å, and c = 28.231 (6) Å. The space group was uniquely determined to be $P2_12_12_1$ with one molecule of $C_{24}H_{32}O_6$ forming the asymmetric unit. All unique diffraction maxima with $2\theta \leq 114°$ were collected on a computer-controlled four-circle diffractometer with graphite monochromated Cu Kα radiation (1.541 78 Å) and a variable speed 1° ω scan. After correction for Lorentz, polarization, and background effects, 1212 (84%) reflections were judged observed ($|F_o| \geq 3\sigma(F_o)$). A phasing model was found by direct methods, and least-squares refinements with anisotropic heavy atoms and isotropic hydrogens have converged to a standard crystallographic residual of 0.0722. A computer-generated perspective drawing of the final X-ray model is given in Figure 1.

It is quite intriguing that the functional array of brianthein W more closely resembles those of the diterpenes found in the sea pen *Scytalium tentaculatum*[5] than it does any previously identified metabolites of either species of *Briareum*. Since the diterpenes of other sea pens, *Ptilosarcus gurneyi*,[6] *Stylatula* sp.,[7] and *Pteroides laboutei*,[8] are much like briarein A and briantheins X, Y, and Z, it is apparent that the secondary metabolism patterns of these organisms are more consonant than their current taxonomic distinction might suggest.

Experimental Section

General procedures, instrumentation, and the collection, extraction and initial chromatographic separation work with *Briareum polyanthes* have been described previously.[2b]

Brianthein W. The CCl_4-soluble extracts of *B. polyanthes*, 3.755 g,[2b] were permeated through Sephadex LH-20 with CH_2Cl_2–hexane (4:1). Fraction 5, 1.2009 g, was permeated through Bio-Beads S-X4 with hexane–CH_2Cl_2–EtOAc (4:4:1). Fraction 5, 382 mg, was subjected to HPLC on an Ultrasphere-Cyano column (0.9 × 25 cm); elution with hexane–isopropyl alcohol (5:1) yielded 119 mg of **3**: prisms from acetone–isooctane, mp 205–209 °C; λ_{max}^{EtOH} 228 nm (ϵ 7500); $\nu_{max}^{CHCl_3}$ 1750 (sh), 1735, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$), δ 5.46 (1 H, br d, J = 8), 5.19 (1 H, br d, J = 5.5), 5.13 (1 H, d, J = 10), 4.86 (1 H, br s), 4.81 (1 H, br s), 2.85 (1 H, br d, J = 15), 2.68 (1 H, m), 2.55 (1 H, m), 2.50 (1 H, dd, J = 15, 6), 2.35–2.10 (2 H, overlapping m), 2.10–1.65 (3 H, obscured m), 2.00, 195, 1.85, 0.97 (each 3 H, s), 1.57 (3 H, br s); ^{13}C NMR (C_6D_6) δ 173.47 (s), 170.38 (s), 170.19 (s), 159.48 (s), 143.24 (s), 136.87 (s), 124.75 (s), 123.64 (d), 116.76 (d), 80.36 (d), 74.47 (d), 72.38 (d), 53.43 (t), 41.48 (s), 37.64 (d), 33.70 (t), 29.22 (t), 27.38 (q), 26.36 (t), 21.48 (q), 20.78 (q), 20.66 (q), 14.48 (q) 9.54 (q); MS, m/z (relative intensity) 416.2213 (M^+, calcd for $C_{24}H_{32}O_6$ 416.2198, <1), 356 (11), 314 (12), 296 (33), 228 (13), 215 (30), 119 (32), 43 (100).

X-ray Diffraction Studies. All crystallographic calculations were done on a PRIME 850 computer operated by the Cornell Chemistry Computing Facility. Principal programs employed were REDUCE and UNIQUE, data reduction programs by M. E. Leonowicz, Cornell University, 1978; MULTAN78, a system of computer programs for the automatic solution of crystal strcutures from X-ray diffraction data (locally modified to perform all Fourier calculations, including Patterson syntheses) written by P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson, University of York, England, 1978; BLS78A, an anisotropic block-diagonal least-squares refinement written by K. Hirotsu and E. Arnold, Cornell University, 1980; PLUTO78, a crystallographic illustration program by W. D. S. Motherwell, Cambridge Crystallographic Data Centre, 1978; and BOND, a program to calculate molecular parameters and prepare tables written by K. Hirotsu, Cornell University, 1978.

Acknowledgment. Work at Montana State University was funded by the Lilly Research Laboratories and a state match to NSF-EPSCOR Grant ISP-8011449. Fieldwork at the Bermuda Biological Station was supported by a grant from the EXXON Foundation. NMR and MS facilities at M.S.U. were developed with funds from the National Science Foundation and the Murdock Foundation. Work at Cornell University was supported by a New York State Sea Grant and NIH CA 24487.

Registry No. **3**, 91178-23-3.

Supplementary Material Available: X-ray data for brianthein W, including (a) Table 1 listing fractional coordinates and thermal parameters, (b) Table 2 listing bond distances, and (c) Table 3 listing bond angles (5 pages). Ordering information is given on any current masthead page.

(4) We have elected to call the briaran diterpenes from *B. polyanthes* "briantheins" to distinguish these compounds and their parent organism taxonomically from *B. asbestinum* and the briareins.

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A New Route to 1,4-Disubstituted Cyclohexa-1,3-diene Derivatives: The Synthesis of a Highly Conjugated Bis(benzothiazoline) Derivative

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Received March 19, 1984

There is currently great interest in the preparation of symmetrical bis(1,3-dithiole) and bis(1,3-thiazoline) derivatives with extended conjugation between the two heterocyclic rings. Some of these are electron donors that form organic metals when complexed with suitable electron acceptors. For example, molecules of types **1**,[1] **2**,[2] **3**,[3] **4**,[4] and **5**[5] have recently been studied. A standard route to these compounds involves condensation of 2 equiv of a 1,2-dithiol or 1,2-amino thiol with 1 equiv of the appropriate dialdehyde or diacid chloride, followed by oxidation to yield the conjugated system. In order to prepare a donor of type **6** we needed the difunctional cyclohexa-1,3-diene derivative **10**.

Cyclohexa-1,3-diene derivatives bearing electron-withdrawing substituents in the 1- and 4-positions are relatively inaccessible and have been reported in only a limited number of cases.[6] They are not available via Birch re-

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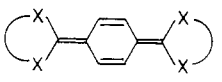
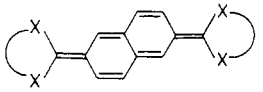
(1)

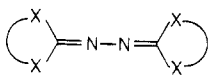
(2)



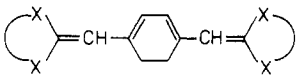
(3)



(4)



(5)



(6)

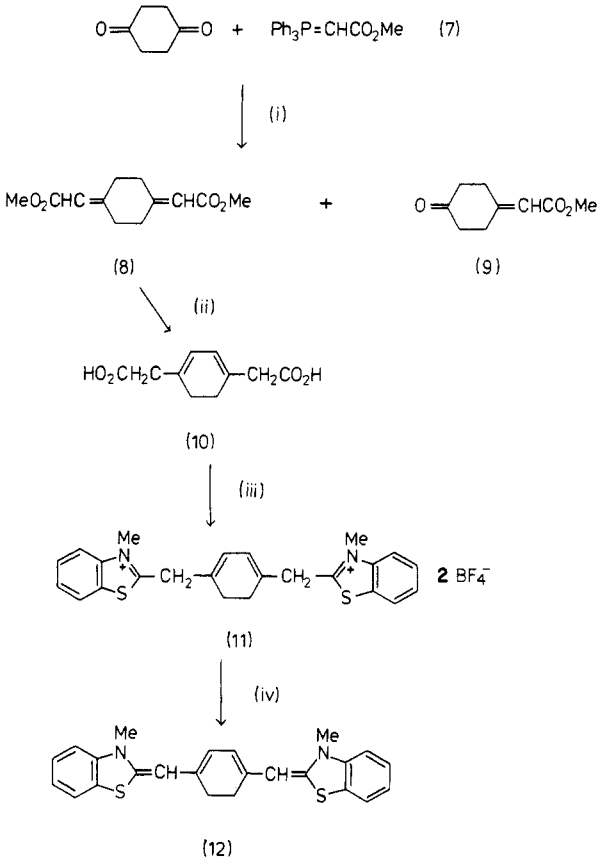
X = S or NR

duction of the corresponding benzene derivative and subsequent double-bond migration, as it is well-known that under Birch reduction conditions electron-withdrawing groups are found on the reduced positions of the 1,4-hexadiene ring.[7] Herein we describe an efficient synthesis of diene **10** from 1,4-cyclohexanedione, offering, to our knowledge, a novel approach to cyclohexa-1,3-diene derivatives. Compound **10** has been converted into the conjugated bis(benzothiazoline) derivative **12**.

Reaction of 1,4-cyclohexanedione with the Wittig reagent **7** yielded diester **8** (Scheme I). A variety of conditions were tried for this reaction: benzoic acid catalysis, following the precedent for reaction of cyclohexanone with **7**,[8] in refluxing benzene or toluene, gave triphenylphosphine oxide and only very low yields of **8** and **9**; potassium carbonate as catalyst in refluxing toluene gave similar results but K_2CO_3 in benzene at 60 °C afforded diester **8** in 70% yield. However, even when an excess of **7** was used some monoketone **9** was always present in the product mixture. Treatment of diester **8** with alcoholic KOH hydrolyzed the ester groups and quantitatively yielded the desired 1,3-cyclohexadiene derivative **10**. UV and NMR spectroscopy confirmed the presence of the conjugated diene system of **10**.

The potential of compound **10** as a difunctional synthon for highly conjugated systems has been demonstrated. Reaction of **10** with oxalyl chloride gave the corresponding

Scheme I[a]



[a] (i) K_2CO_3, benzene, 60 °C; (ii) KOH, methanol, reflux; (iii) oxalyl chloride, chloroform 50 °C; *N*-methyl-*o*-aminothiophenol, chloroform, 20 °C; trityl tetrafluoroborate, acetonitrile, 20 °C. (iv) triethylamine, acetonitrile, 20 °C

diacid chloride which was not purified but reacted directly with *N*-methyl-*o*-aminothiophenol. The product mixture on treatment with triphenylcarbenium tetrafluoroborate yielded dication **11** in moderate yield. Deprotonation of **11** using triethylamine afforded the conjugated bis(benzothiazoline) derivative **12** in high yield.

Experimental Section

^1H NMR spectra were recorded at 40 °C by using either a Varian A56/60D or a Bruker HX90E spectrometer with tetramethylsilane as reference. IR spectra were recorded on a Perkin-Elmer 577 instrument. UV spectra were recorded on a Pye Unicam SP8-100 spectrophotometer. Column chromatography was performed on alumina Brockman activity II.

1,4-Bis(carbomethoxymethylene)cyclohexane (8) and 4-(Carbomethoxymethylene)cyclohexanone (9). A mixture of 1,4-cyclohexanedione (2.25 g, 0.02 mol), ester **7**[9] (26.7 g, 0.08 mol), and potassium carbonate (0.10 g) in benzene (100 mL) was heated at 60 °C for 12 h. The mixture was cooled and filtered and solvent was removed in vacuo. Ether (150 mL) was added to the residual solid and triphenylphosphine oxide was separated by filtration. The filtrate was adsorbed onto alumina and chromatographed on an alumina column. Elution with hexane–ether (4:1 v/v) yielded diester **8** (3.8 g, 70%) as white needles: mp 85–88 °C (from methanol); IR (Nujol) 1712 (C=O), 1645 (C=C), 1258 1232, 1165, 1020, 862, 712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.3–3.2 (AB, 8 H), 3.70 (s, 6 H), 5.80 (s, 2 H). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.3; H, 7.1. Found: C, 64.3; H, 7.4. Continued elution gave compound **9** (0.34 g, 10%) as white crystals: mp 40–45 °C (from methanol); IR (Nujol) 1700 (C=O), 1635 (C=C), 1260, 1208, 1165, 972, 860, 728

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cm^{-1}; ^1H NMR ($CDCl_3$) 2.4–3.4 (AB, 8 H), 3.65 (s, 3 H), 5.80 (s, 1 H). Anal. Calcd for $C_9H_{12}O_3$: C, 64.3; H, 7.1. Found: C, 64.1; H, 7.0.

1,4-Bis(carboxymethyl)cyclohexa-1,3-diene (10). Diester 8 (2.24 g, 0.01 mol) was refluxed for 1 h in methanol (60 mL) containing potassium hydroxide (2.0 g). Solvent was then removed in vacuo, and the resulting viscous oil was dissolved in water. Acidification with dilute HCl precipitated white crystals of diene 10 (1.90 g, 97%): mp 184–188 °C; IR (Nujol) 1690, 1330, 1230, 1142, 920, 770 cm^{-1}; ^1H NMR [$(CD_3)_2CO$] δ 2.26 (s, 4 H), 3.07 (s, 4 H), 5.70 (s, 2 H); UV (CH_3OH) 262 nm. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.2; H, 6.1. Found: C, 60.9; H, 6.3.

Preparation of Bis(benzothiazolinium) Derivative 11. Oxalyl chloride (1.30 g, 10 mmol) was added dropwise with stirring to a solution of diacid 10 (1.0 g, 5 mmol) in dry chloroform under nitrogen. The solution was held at 50 °C for 2 h, and then solvent was removed in vacuo to yield 1.23 g of the diacid chloride as a viscous oil [IR (film) 1800 (C=O) cm^{-1}]. This oil was dissolved in dry chloroform (20 mL) and added dropwise to a solution of *N*-methyl-*o*-aminothiophenol[10] (1.4 g, 10 mmol) in dry chloroform (20 mL). The solution was stirred at room temperature for 12 h under nitrogen and then a solution of excess triphenylcarbenium tetrafluoroborate in acetonitrile was added to precipitate dication 11 as a buff powder. Recrystallization from acetic acid/water gave 1.41 g [48% based on diacid 10] as buff crystals: mp >290 °C; ^1H NMR (CF_3COOH) δ 2.10 (s, 4 H), 3.93 (s, 4 H), 3.98 (s, 6 H), 5.88 (s, 2 H), 7.30–7.80 (m, 8 H). Anal. Calcd for $C_{24}H_{24}N_2S_2B_2F_8$: C, 49.8; H, 4.2; N, 4.8. Found: C, 50.1; H, 4.0; N, 5.2.

Preparation of Bis(benzothiazoline) Derivative 12. To a suspension of dication 11 (578 mg, 1.0 mmol) in acetonitrile (15 mL) was added an excess of triethylamine. The mixture was stirred at room temperature for 12 h. Evaporation of the solvent yielded a brown solid which was purified by column chromatography on alumina with diethyl ether as eluent. Compound 12 (320 mg, 80%) was obtained as orange crystals: mp 212–213 °C; ^1H NMR [$(CD_3)_2SO$] δ 2.31 (s, 4 H), 5.50 (s, 2 H), 5.80 (s, 2 H), 7.12–7.80 (m, 8 H). Anal. Calcd for $C_{24}H_{22}N_2S_2$: C, 71.6; H, 5.5; N, 7.0. Found: C, 71.3; H, 5.9; N, 7.2.

Registry No. 8, 91158-09-7; 9, 91158-10-0; 10, 91158-11-1; 10 (diacid chloride), 91158-14-4; 11, 91158-12-2; 12, 91158-13-3; $Ph_3P{=}CHCO_2Me$, 2605-67-6; 1,4-cyclohexanedione, 637-88-7; *N*-methyl-*o*-aminophenol, 21749-63-3.

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The Bromination of 2-Phenyl-2*H*-indazole. Formation and Structure Determination of Mono-, Di-, and Tribromo-2-phenyl-2*H*-indazoles[1]

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Received November 30, 1983

Electrophilic substitution of azoles[4] is a complex reaction where reaction conditions considerably modify product orientation. The situation is even more complex for benzazoles as is illustrated by the results of electrophilic aromatic substitution reactions of 1*H*-indazole.[5-8] Bromination of 1*H*-indazole in dilute acid gives 3,5-dibromo-1*H*-indazole,[9] sulfonation affords 1*H*-indazole-7-sulfonic acid,[10] and nitration in sulfuric acid gives 5-nitro-1*H*-indazole,[11] whereas from the nitration in acetic acid/acetic anhydride a mixture of 3-nitro- and 3,5-dinitro-1*H*-indazole,[2] is obtained. Moreover substituents quite often exercise effects different from their effects on electrophilic aromatic substitution in benzene. A typical example being the ortho nitration of 6-nitro-1*H*-indazole to 5,6-dinitro-1*H*-indazole.[2,12,13]

Scheme I

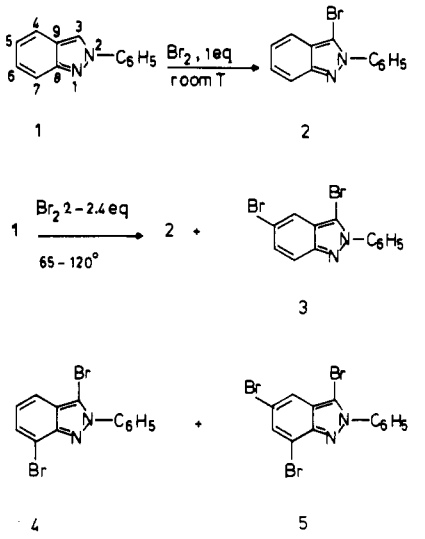

Table I. Bromination Procedures[a] and Yields (relative mole %)[e]

	1			2
	1.0 equiv Br_2[b] 20 °C	2.4 equiv Br_2[c] 120 °C	2.0 equiv Br_2[c] 65 °C	1.0 equiv Br_2[d] 120 °C
2	100	33	52	47
3		39	27	32
4		24	18	19
5		4	3	2
total rel %	100	100	100	100
actual yield %	88.6	86.8	91.7	75.2

[a] A 1–2 N Br_2 solution in acetic acid was slowly dropped into a solution of 1 g of 1 or 2 in 25 mL of acetic acid. [b] Addition time, 3.5 h. [c] Addition time, 12 h. [d] Addition time, 8 h. [e] Separated by column chromatography (see Experimental Section).

(1) This is Part 3 of our Indazole Studies. For preceding studies see ref 2 for Part 1 and ref 3 for Part 2.
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(13) (a) In contrast to what is described in ref 5 and 8 nitration of 6-nitro-1*H*-indazole gives 5,6-dinitro-1*H*-indazole whereas nitration of 5-nitro-1*H*-indazole affords 5,7-dinitro-1*H*-indazole; see ref 2 and 12. (b) When indazole has an unsubstituted NH group there is the possibility of tautomerism and to our knowledge 1*H*- and 2*H*-tautomers have never been isolated as separate compounds, although they may enter chemical reactions predominantly in one form. An indication that the exchange of the NH proton is so fast that the "tautomeric mixture" behaves magnetically as a single compound is evident from the proton magnetic resonance spectra of these indazoles exhibiting a one-proton signal for H-3. For indazoles designated either as 1*H*- or 2*H*-indazoles the existence and therefore the participation in reactions of the other tautomer is understood.

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