in these cases alternate methods of analysis could be employed.[15]

Interestingly, Pettit recently speculated that the glutamine thiazole present in dolastatin, a cytotoxic peptide isolated from a marine mollusc, has the *S* configuration on the grounds that *S* is the natural configuration.[16] Our results certainly indicate that such speculation should be avoided.

Acknowledgment. This study was supported by a grant from the National Institutes of Health (CA 29821). ^{1}H NMR spectra were obtained on the Bruker HX-270 spectrometer at the Northeast Regional NSF-NMR Facility, Yale University, partially supported by the National Science Foundation (Grant CHE 79-16210).

Registry No. 3, 86024-29-5; 4, 74847-09-9; 5, 81120-73-2; 6, 81098-23-9; 7, 81120-74-3.

(15) Pirkle, W. H.; Finn, J. M.; Schreiner, J. L.; Hamper, B. C. *J. Am. Chem. Soc.* **1981**, *103*, 3964.
(16) Pettit, G. R.; Kamano, Y.; Brown, P.; Gust, D.; Inoue, M.; Herald, C. *J. Am. Chem. Soc.* **1982**, *104*, 905-7.

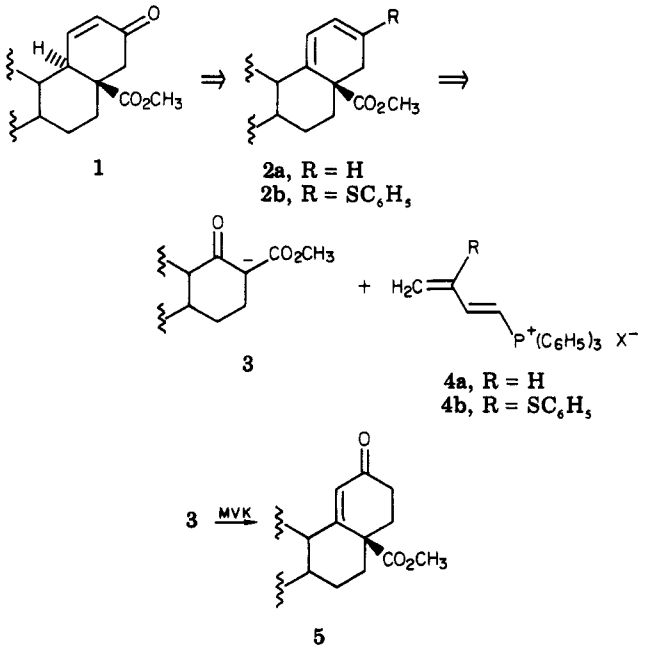
Joseph E. Biskupiak, Chris M. Ireland*
Section of Medicinal Chemistry and Pharmacognosy
School of Pharmacy, University of Connecticut
Storrs, Connecticut 06268
Received March 29, 1983

The Robinson Transposition Reaction.[1] Conjugate-Addition/Intramolecular Wittig Reactions of Enolates with [3-(Phenylthio)-1,3-butadienyl]triphenylphosphonium Chloride

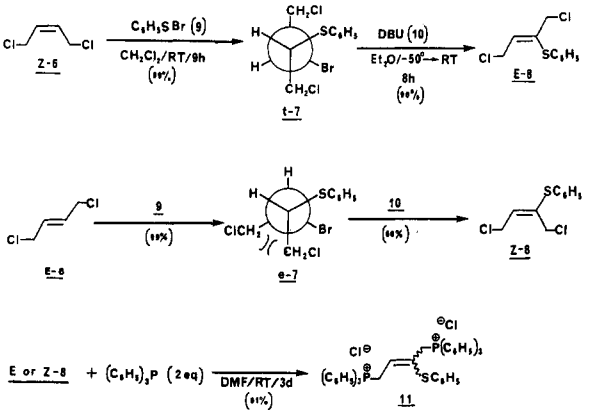
Summary: The phosphonium salt described reacts with certain enolates to produce dienyl sulfides that may be subsequently hydrolyzed to afford enones that are regiotransposed relative to the standard Robinson annulation product.

Sir: During the course of one of our synthetic projects we required a functionalized enone of the general structure **1** (Scheme I). As can readily be seen, **1** is a transposed version of the enone **5** routinely prepared via the Robinson annulation process. Although it seems reasonably likely that transformation of **5** to **1** would be possible,[2] we wished to effect a more direct conversion of **3** to enone **1**. Previous experience by Büchi[3a] and ourselves[3b] concerning the conjugate addition of ketone enolates **3** to butadienyl phosphonium salt **4a** affording cyclohexadienes (**2a**) after an intramolecular Wittig reaction, led us to conclude that a [3-(phenylthio)-1-butadienylphosphonium salt (**4b**) should similarly afford a dienyl sulfide (**2b**) capable of hydrolysis to the requisite transposed enone **1**.[4,5]

Scheme I



Scheme II



Synthesis of an appropriate reagent (albeit not **4b** as a discrete and isolable substance) was accomplished as follows (Scheme II): Reaction of (*Z*)-1,4-dichlorobut-2-ene ((*Z*)-**6**) with phenylsulfenyl bromide (**9**) (generated by the reaction of diphenyl disulfide with bromine in methylene chloride[6]) affords *threo*-trihalo sulfide **t-7**[7,8] in essentially quantitative yield as a colorless oil. Similarly the isomeric dichloride (**E**)-**6** reacts with **9** to produce crystalline *erythro*-trihalo sulfide **e-7** (99% as oil, 77% as crystals, mp

(1) Bruceantin Support Studies. 3. For paper 2, see S. N. Suryawanshi, P. L. Fuchs, *Tetrahedron Lett.*, 4201 (1981).
(2) In point of fact, Watt et al. have attempted a Robinson annulation reaction on a substrate bearing functionality appropriate for Bruceantin synthesis. Although the Michael reaction proceeds smoothly, in this instance the intramolecular aldol/dehydration sequence fails completely. D. L. Snitman, M. Y. Tsai, D. S. Watt, *Synth. Commun.*, **8**, 195 (1978). See also: Pariza, R. J.; Fuchs, P. L. *J. Org. Chem.*, following paper in this issue.
(3) (a) G. Büchi, M. Pawlak, *J. Org. Chem.*, **40**, 100 (1975); (b) P. L. Fuchs, *Tetrahedron Lett.*, 4055 (1974).
(4) Other 4C + 2C approaches to heteroatom-substituted dienes have been reported by Martin. (a) The reaction of a (2-alkoxy)dienylphosphonium salt with ketone enolates to afford, after hydrolysis, an enone bearing the Robinson substitution pattern: S. F. Martin, S. R Desai, *J. Org. Chem.*, **43**, 4673 (1978). (b) The reaction of a [1-(methylthio)dienyl]phosphonate to afford noncyclized dienyl sulfides after *inter*molecular Wadsworth-Emmons reaction with a second carbonyl component: S. F. Martin, P. J. Garrison, *Synthesis*, 394 (1982).
(5) A 3C + 3C annulation approach to enones via conjugate addition of (2-alkoxyallylidine)triphenylphosphorane to enones followed by intramolecular Wittig reaction to yield a dienyl ether has been reported by Martin and Desai (S. F. Martin and S. R. Desai, *J. Org. Chem.*, **42**, 1664 (1977)).
(6) B. M. Trost and S. D. Ziman, *J. Org. Chem.*, **38**, 933 (1973).
(7) All new compounds have been characterized by a combination of ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, IR, mass spectrometry, and/or combustion analysis. Yields refer to material of greater than 95% purity.
(8) Experimental details, including 360- and 470-MHz ^{1}H NMR and ^{13}C NMR spectral evidence for compounds **t-7**, (*E*)-**8**, **11**, **18**, and **19** are in the supplementary material.

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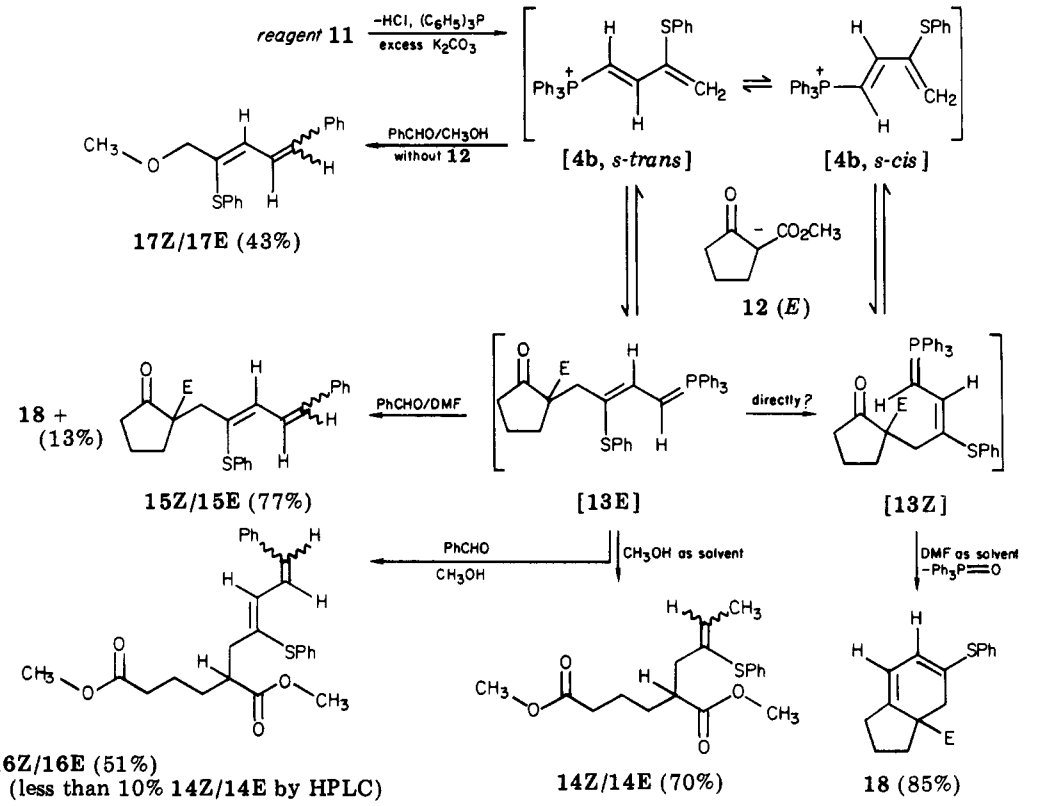
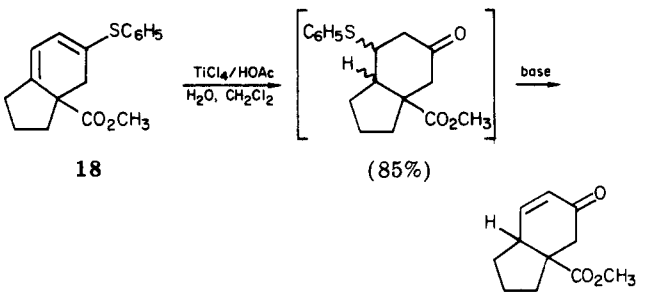
Scheme III



68–68.5 °C. Treatment of **t-7** with DBU, **10** (1,8-diazabicyclo[5.4.0]undec-7-ene) at −50 °C in ether, followed by allowing the solution to gradually warm to room temperature, smoothly affords the *E*-dichlorovinyl sulfide (*E*)-**8**. The DBU elimination of HBr from **e-7** is less efficient than from **t-7**, yielding recovered starting material (**e-7**), some (*E*)-1-chloro-3-(phenylthio)-1,3-butadiene,[7,9] and (*Z*)-dichlorovinyl sulfide (*Z*)-**8**[7] (60%). Treatment of *either* (*Z*)-**8** or (*E*)-**8** with 2.2 equiv of triphenylphosphine in DMF at 25 °C for 3 days affords the same bis(phosphonium) salt **11**[7,8] (61%; P_a = 21.36, P_b = 22.31 ppm, relative to external H_3PO_4; $^5J_{PP}$ = 11.35 Hz; mp 164–166 °C). The stereochemistry at the double bond is uncertain.[3a] Attempts to intercept a monophosphonium salt by using only 1 equiv of triphenylphosphine lead to lower yields of **11**. Mechanistic studies on this sequence will be reported in due course.

Slow addition (3–5 h) of a DMF solution of reagent **11** (1.07 equiv) to a solution of 2-(carbomethoxy)cyclopentanone (**12**) in the presence of excess (2.9 equiv) dry, pulverized K_2CO_3, at 25 °C under N_2, produces an orange to red solution. Workup (a few drops of 30% H_2O_2, cold, to convert the liberated triphenylphosphine to triphenylphosphine oxide; hexane vs. water extraction) affords dienyl sulfide **18**[7,8] in 85% yield and high purity. Further purification can be accomplished by flash chromatography or bulb-to-bulb distillation. Table I lists a number of substrates along with the products, yields, and temperatures of the reactions, all of which are conducted as in the above example. Although a detailed study of these reactions was neither desired nor undertaken, several salient points require brief comment.

Scheme IV

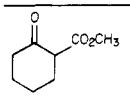
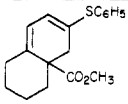
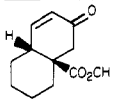
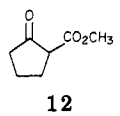
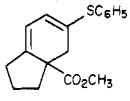
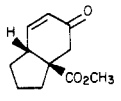
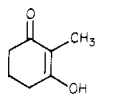
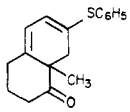
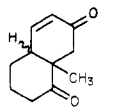
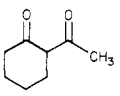
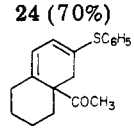
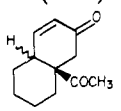
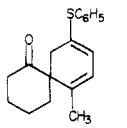
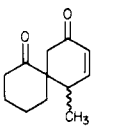
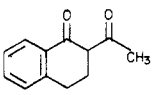
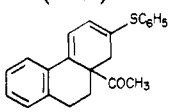
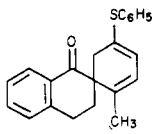
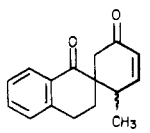


Use of methanol as solvent or including benzaldehyde (1.3 equiv) in the reaction media with substrate **12** in DMF produces vinyl sulfides **14Z/14E**[7,10] or dienyl sulfides **15Z/15E**[7], respectively (see Scheme III). Furthermore, when benzaldehyde (1.1 equiv) is present and methanol is used as the solvent, intermediate **13E** is trapped by the benzaldehyde, and the resulting 2,2-disubstituted β-keto ester undergoes ring-opening methanolysis to yield **16Z/16E**[7]. Less than 10% of **14Z/14E** was detected by HPLC or ^1H NMR in the **16Z/16E** product mixture despite the fact that nearly 300 equiv of methanol were present, compared with only 1.1 equiv of benzaldehyde. When methanol is used as solvent (200–300 equiv) in the presence of benzaldehyde (1.1 equiv) and 2-methyl-1,3-cyclohexanedione, **23**, is the substrate, only **17Z/17E**,[7] the products of addition of methoxide to **4b** followed by benzaldehyde trapping, are isolated.

(9) (*E*)-1-Chloro-3-(phenylthio)-1,3-butadiene can be made in 90% yield as a distilled oil from either (*Z*)-**8** or (*E*)-**8** and DBU/ether at room temperature ($^3J_{HH}$ = 13 Hz, C_6D_6, coincidental in $CDCl_3$). This elimination pattern is similar to that found by Bridges and Fischer A. J. Bridges and J. W. Fischer, *Tetrahedron Lett.*, **24**, 445, 447 (1983) with 1,2,4-trihalo-3-(phenylthio)-2-butenes.

(10) Presumably the alcohol serves to protonate intermediate allyl ylide [(*E*)-**13**] to allyl phosphonium salt, which undergoes alkoxide-catalized cleavage to vinyl sulfide **14Z/14E**. The presence of **14Z** may indicate direct double-bond isomerization (see text). For cleavage of phosphonium salts, see G. Aksnes, *Phosphorus Sulfur*, **3**, 227 (1977), and references cited therein.

Table I

substrate	temp,[a] °C	dienyl sulfide	enone
 20	25	 21 (75%)	 22 (68%)
 12	25	 18 (85%)	 19 (75%)
 23	80	 24 (70%)	 25 (50%)
 26	80	 27F (46%)	 28F (53%)
		 27S (40%)	 28S (81%)
 29	60[b]	 30F (4%)	
		 30S (66%)	 31S (35%)

[a] The temperatures are given for the annulation step. [b] ~10% fused diene is formed at 110 °C.

Since **13E** is incapable of intramolecular cyclization for geometrical reasons a mechanism for conversion to the *Z* isomer (**13Z**) is necessary to explain the Wittig product **18**. Although we favor a mechanism involving reversion of **13E** to **4b** followed by readdition to the s-cis form of the reagent, on the basis of our earlier observations with the unsubstituted reagent **4a**,[3b] a direct interconversion of **13E** to **13Z** via protonation/deprotonation of the allyl ylide moiety also remains a possibility.[3a,10]

The dienyl sulfides shown in Table I were converted to enones in fair to good yield by Ti(IV)-mediated hydrolysis.[11] The liberated thiophenol had a tendency to add to the enone under these conditions, as shown in *Scheme* IV. A water wash of the CH_2Cl_2 solutions followed by drying (K_2CO_3) and treatment with base (DBU) produced the enones, which were purified by extraction (H_2O vs. CH_2Cl_2 solutions) and chromatography.

The use of reagent **11** followed by hydrolysis of the dienyl sulfide thus provides a sequence that is analogous to the Robinson annulation[12] but yields transposed enones as illustrated.

(11) T. Mukaiyama, K. Kamio, S. Kobayashi, and H. Takai, *Bull. Chem. Soc. Jpn.*, 3723 (1972).

(12) For recent reviews of the Robinson annulation reaction, see M. E. Jung, *Tetrahedron*, **32**, 3 (1976); R. E. Gawley, *Synthesis*, **76**, 777 (1976).

Acknowledgment. We thank the National Institutes of Health for support of this research (Grant No. CA-21840). The ^{13}C NMR and ^{31}P NMR spectrometer used in this investigation was provided by NSF Grant 7841. We also thank the Purdue Biological Magnetic Resonance Laboratory (NIH RR01077) for access to the 360- and 470-MHz ^1H NMR spectrometers and John Saddler and Phil Hamann for providing those spectra.

Registry No. (*Z*)-**6**, 1476-11-5; (*E*)-**6**, 110-57-6; **t-7**, 85335-83-7; **e-7**, 85335-84-8; **8E**, 85335-85-9; **8Z**, 85335-86-0; **9**, 28074-23-9; **11**, 85335-87-1; **12**, 10472-24-9; **14E**, 85335-88-2; **14Z**, 85335-89-3; **15E**, 85336-08-9; **15Z**, 85336-09-0; **16E**, 85335-90-6; **16Z**, 85335-91-7; **17E**, 85335-92-8; **17Z**, 85335-93-9; **18**, 85335-96-2; **19**, 85335-97-3; **20**, 41302-34-5; **21**, 85335-94-0; **22**, 85335-95-1; **23**, 32774-63-3; **24**, 85335-98-4; **25**, 85335-99-5; **26**, 874-23-7; **27F**, 85336-00-1; **27S**, 85336-02-3; **28F**, 85336-01-2; **28S**, 85336-03-4; **29**, 17216-08-9; **30F**, 85336-04-5; **30S**, 85336-05-6; **31S**, 85336-06-7; (*E*)-1-chloro-3-(phenylthio)-1,3-butadiene, 85336-07-8.

Supplementary Material Available: Experimental details for compounds **t-7**, (*E*)-**8**, **11**, **18**, and **19** (6 pages). Ordering information is given on any current masthead page.

[†] Graduate Research Associate.

R. J. Pariza,[†] P. L. Fuchs*
Department of Chemistry
Purdue University
West Lafayette, Indiana 47907
Received December 28, 1982

Rapid Access to a Highly Functionalized Tricyclic Bruceantin Intermediate[1]

Summary: Having found several B → (AB or BC) → ABC ring-formation strategies unsuited for the synthesis of bruceantin and other quassinoids, we have successfully produced a highly functionalized intermediate, of desired stereochemistry, from a C → [BC] → ABC approach. The chemistry is briefly discussed, and full experimental details are available.

Sir: The potent cytotoxic properties[2] and dense array of functionality present in the quassinoid bruceantin (**1**, Scheme I) have elicited considerable medicinal and synthetic interest.[3] Unfortunately, preliminary results from phase-two clinical trials in humans have not been overly encouraging; although bruceantin exhibits exceptionally low human toxicity, it has produced only marginally beneficial effects in a number of tumor systems.[4] For this reason it is essential to develop a bruceantin synthesis capable of providing analogues *in sufficient quantity* for further clinical evaluation.

Watt has discussed a synthetic approach to bruceantin (**1**) that utilizes a B → AB → ABC strategy wherein the AB fragments **2a** and **2b** were prepared via the Robinson annulation protocol from 2-methylcyclohexane-1,3-dione

(1) Bruceantin Support Studies. 5. For paper 4, see: Pariza, R. J.; Kuo, F.; Fuchs, P. L. *Synth. Commun.* **1983**, *13*, 243.

(2) (a) Kupchan, S. M.; Britton, R. W.; Ziegler, M. F.; Siegel, C. W. *J. Org. Chem.* **1973**, *38*, 178. (b) Kupchan, S. M.; Britton, R. W.; Lacadie, J. A.; Ziegler, M. F.; Siegel, C. W. *Ibid.* **1975**, *40*, 648.

(3) For studies directed toward the synthesis of bruceantin and other quassinoids, see: Kraus, G. A. J. Org. *Chem.* **1982**, *47*, 4271 and references cited therein.

(4) Personal communication from Dr. Mathew Suffness, National Cancer Institute.

0022-3263/83/1948-2306$01.50/0