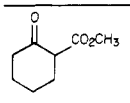
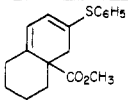
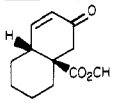
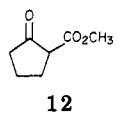
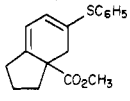
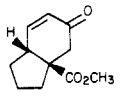
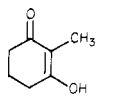
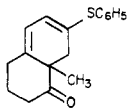
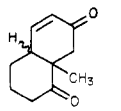
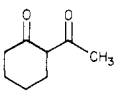
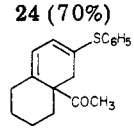
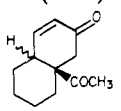
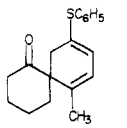
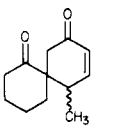
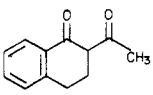
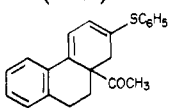
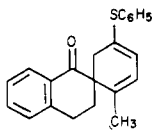
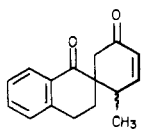
Table I

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.

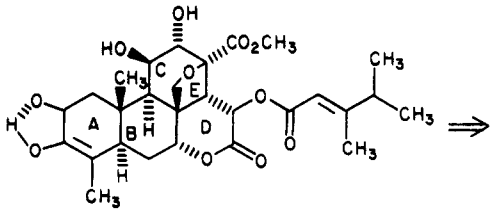
(2) (a) Kupchan, S. M.; Britton, R. W.; Ziegler, M. F.; Siegel, C. W. *J. Org. Chem.* **1973**, *38*, 178. (b) Kupchan, S. M.; Britton, R. W.; Lacadie, J. A.; Ziegler, M. F.; Siegel, C. W. *Ibid.* **1975**, *40*, 648.

(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.

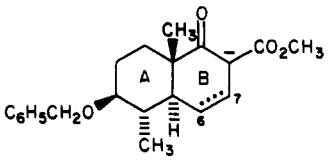
(4) Personal communication from Dr. Mathew Suffness, National Cancer Institute.

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

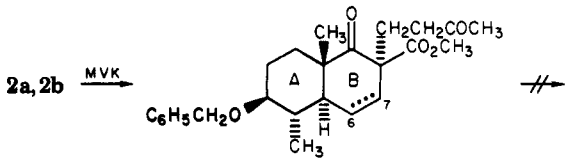
Scheme I



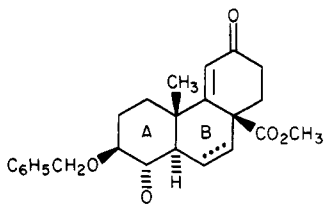
1



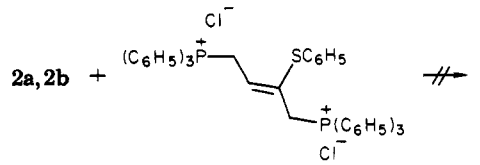
2a ($\Delta^{6,7}$ saturated)
2b ($\Delta^{6,7}$ unsaturated)



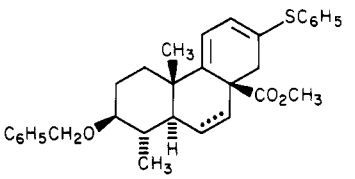
3a ($\Delta^{6,7}$ saturated)
3b ($\Delta^{6,7}$ unsaturated)



4a ($\Delta^{6,7}$ saturated)
4b ($\Delta^{6,7}$ unsaturated)

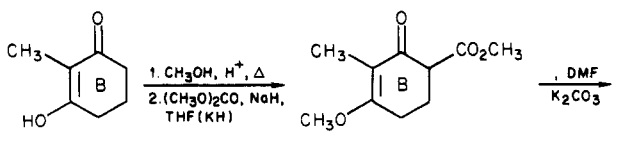


5

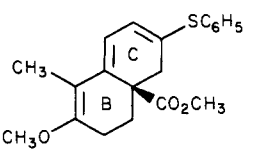


6a ($\Delta^{6,7}$ saturated)
6b ($\Delta^{6,7}$ unsaturated)

Scheme II



7 8



9

as the B-ring precursor.[5a] Unfortunately conversion of **2a** and **2b** to tricyclic enones **4a** and **4b** by a second Robinson annulation sequence was foiled by the reluctance of 1,5-diketones **3a** and **3b** to undergo the intramolecular aldol/dehydration reaction.[5]

Equally unsatisfactory was our attempt at construction of the C ring of tricyclic dienyl sulfides **6a** and **6b** by a Robinson transposition reaction[6] using reagent **5**[6] with keto esters **2a** and **2b**. Clearly, in both instances the steric constraints imposed by the bis(tertiary) B-ring carbonyl have effectively overridden the entropic advantage usually afforded by an intramolecular ring closure.

In an attempt to circumvent this problem, we next examined a B → BC → ABC approach. Namely, sequential treatment of 2-methylcyclohexane-1,3-dione (**7**, Scheme II) with acidic ethanol[7a,b] followed by acylation of the resulting vinylogous ester with diethyl carbonate and sodium hydride (using the catalytic potassium hydride method of Deslongchamps[8]) afforded ester **8** in 40% overall yield. Armed with the hypothesis that changing the hybridization of the B ring of **8** would allow the requisite intramolecular Wittig reaction to proceed with greater facility than was observed with the corresponding aldol reaction, we subjected ester **8** to the action of reagent **5**[6] in the presence of anhydrous potassium carbonate in DMF at 115 °C. The desired reaction did occur to afford trienylsulfide **9**,[9a] but the yield was a disappointing 18%. Modification of the conditions by slow addition of the reagent in DMF (115 °C) over 12 h to a solution of **8** and anhydrous potassium carbonate only served to increase the yield of 24.4%.

Faced with the impracticability of material supply via the **7** to **9** transformation but encouraged by the beneficial effect of sp^2 hybridization at the ring juncture, we elected to further modify the approach to a C → [BC] → ABC strategy. Treatment of the readily available keto ester **10**[10] with ethyl vinyl ketone or 1-chloro-3-pentanone[11] in methanol (Scheme III), in the presence of base, resulted in the facile synthesis of the monoannulated ester **11** (K_2CO_3, room temperature, 85.6%, mp 99–100 °C) or the bis(annulated) acid **12**, (sodium methoxide, reflux, 60% in one pot, 0.5-mol scale; mp 161–163 °C).[9b] The latter process presumably involves the intermediacy of lactone **[13]** to account for the hydrolysis of the ester and the

(5) (a) Snitman, D. L.; Tsai, M.-Y.; Watt, D. S. *Synth. Commun.* **1978**, *8*, 95. (b) Spencer, T. A.; Friary, R. J.; Schmiegel, W. W.; Simeone, J. F.; Watt, D. S. *J. Org. Chem.* **1968**, *33*, 719.

(6) Pariza, R. J.; Fuchs, P. L. *J. Org. Chem.*, previous communication in this issue.

(7) (a) Pirung (Pirung, M. C. *J. Am. Chem. Soc.* **1981**, *103*, 82) improved the procedure in ref 7b by use of 3-Å sieves in a Soxhlet, 84% yield. (b) McCullough, J.; Kelly, J.; Rasmussen, P. *J. Org. Chem.* **1969**, *34*, 2933. (c) Fuchs, P. L.; Bunnell, C. A. "Carbon-13 NMR Based Organic Spectral Problems"; Wiley: New York, 1979; problem 25.

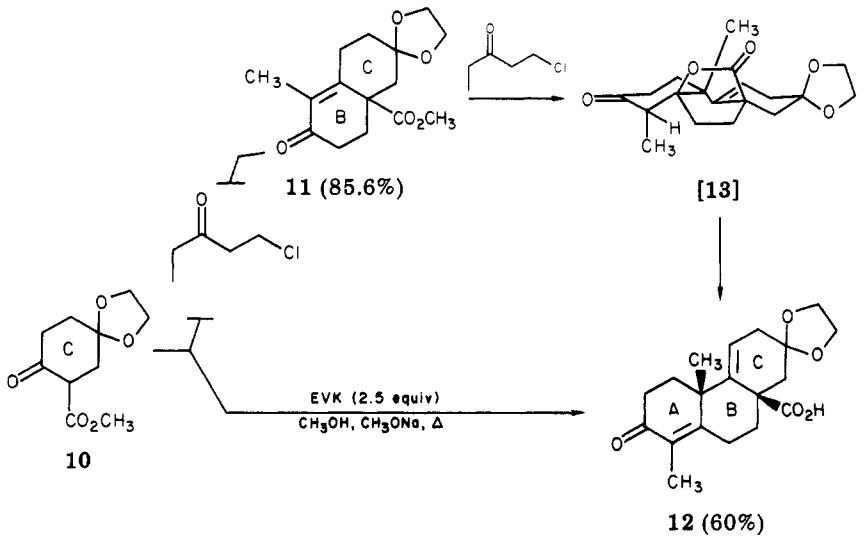
(8) Ruest, L.; Boulin, G.; Deslongchamps, P. *Synth. Commun.* **1976**, *6*, 169.

(9) (a) Compound **9** shows an ester carbonyl in the IR spectrum at 5.79 μm as well as the absence of a vinylogous ester carbonyl in the ^{13}C NMR spectrum (193–199 ppm), which distinguishes the fused-ring isomer shown from the possible spiroannulated product.[6] A full discussion of the spectral arguments is given in the supplementary material.[9c] (b) Carbon T_1 measurements (Varian XL-200 Inversion–Recovery Sequence; 0.3–0.5 M/$CDCl_3$ at 25 °C) of **12** and **14** indicate that **12** (as the hemihydrate per combustion analysis; mp 161–163 °C from ethyl acetate) exists as a dimer in solution. Dutta et al.[13] reported **12** as a monohydrate (mp 200 °C from ethyl acetate). (c) Full experimental and spectral data for compounds **8–12** and **14**, including carbon T_1 measurements for **12** and **14**, can be found in the supplementary material.

(10) See ref 1 for an improved synthesis of **10**.

(11) Prepared by addition of excess ethylene to propionyl chloride (7.0 mol) in CH_2Cl_2 (2.5 L) containing $AlCl_3$ (7.7 mol) at 0–5 °C. After aqueous workup, 82–91% yields of distilled (bp, 61–65 °C (20 mm), $n^{23}D$ 1.4325) materials were obtained, which were pure by ^1H NMR. See: Halsall, T. G.; Theobald, D. W.; Walshaw, R. B. *J. Chem. Soc.* **1964**, 1029.

Scheme III



isolation of only one isomer.[12,13] The tricyclic acid **12** can initially be obtained as the sodium salt, which is convenient for direct reesterification (**14**, CH_3I, DMF, room temperature, 98%; mp 129–130 °C)[9b] and is readily converted to the acid (aqueous buffer to pH 5, >90% after crystallization). Compounds **11–14** have been reported by Dutta et al.,[13] who demonstrated the stereochemistry of **12** and **14** by isolating **13** and converting it to **14**. The conditions, yields, and analytical data[9b,c] in the present work represent a notable advancement. Further work using these potentially valuable intermediates in bruceantin and quassinoid syntheses is under way.

Acknowledgment. We thank the National Institutes of Health for support of this research (Grant CA-21840). The Varian XL-200 spectrometer used in this investigation was provided by NSF Grant 7841. We are grateful to the Purdue University Biological Magnetic Resonance Laboratory (NIH RR 01077) for access to the 470-MHz ^1H NMR spectrometer and Phil Hamann for providing those spectra. We also thank Professor David Watt for generous samples of the keto esters **2a** and **2b** and F. Kuo for work on the esterification of **12**.

Supplementary Material Available: Experimental procedures used and analytical data for compounds **8–12** and **14** (9 pages). Ordering information is given on any current masthead page.

(12) Snitman, D. L.; Watt, D. S. *Synth. Commun.* **1978**, *8*, 187. Snitman, D. L.; Himmelsback, R. J.; Watt, D. S. *J. Org. Chem.* **1978**, *43*, 4758.

(13) Mukherjee, D.; Mukhopadhyay, S. K.; Mahalanabis, K. K.; Gupta, A. D.; Dutta, P. C. *J. Chem. Soc., Perkin Trans. 1*, **1973**, 2083.

† Graduate Research Associate.

R. J. Pariza,† P. L. Fuchs*

Department of Chemistry
Purdue University
West Lafayette, Indiana 47907

Received February 28, 1983