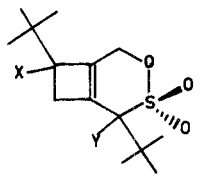
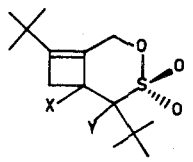


4

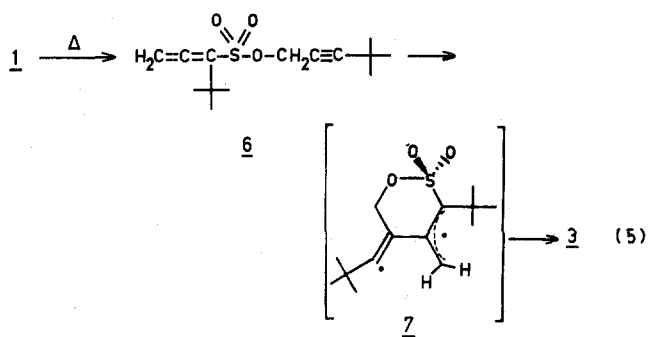


5

a. X = Y = Br
b. X = H, Y = I
c. X = H, Y = OH
d. X = Y = H

duct **4b** or **5b** is obtained with HI; this on treatment with $AgNO_3$ in THF–water affords unstable **4c** or **5c**. Treatment with triethylamine causes **4/5a** to revert to **3** whereas **4/5b** and **4/5c** revert to **3** on chromatography. Hydrogenation of **3** (Pd/C) gives a complex mixture of reduced products; reduction (Zn/HOAc) of **4/5b** gives **4/5d**. Ozonolysis of **3** produces a stable ozone addition product, mp 83.3–83.8° dec, the structure of which is under investigation.[10]

The structure of **3** makes probable that it is preceded by **6**, which we have been unable to observe, suggesting its great proclivity toward cycloaddition, even through the uncommon allene–acetylene mode.[11] It is likely that the latter reaction passes through diradical **7** (eq 5).[11a] A superficially



(5)

related reaction has been observed by Braverman and Segev.[2a] The structure **2** originally considered as an alternative would become accessible were **6** to undergo a subsequent [3,3] sigmatropic rearrangement (eq 3), followed by the well-known allene dimerization through a 2,2′-bisallyl diradical.[6,11g]

Further investigations are underway.

Acknowledgment. We are indebted to Professor Dr. A. Vos of the Department of Structural Chemistry of this university for making available equipment for crystallographic work.

Supplementary Material Available. A listing of crystallographic data (atomic coordinates and thermal parameters, interatomic distances, bond angles and least square planes) as well as physical data for **3**, **4/5a-d** and the ozone adduct will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journal Division, American Chemical Society, 1155 16th Street, N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-3308.

References and Notes

(1) (a) S. Braverman and Y. Stabinsky, *Chem. Commun.*, 270 (1967); *Isr. J. Chem.*, **5**, 125 (1967). (b) P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, and K. Mislow, *J. Am. Chem. Soc.*, **90**, 4869 (1968). (c) R. Tang and K. Mislow, *ibid.*, **92**, 2100 (1970). (d) Also D. H. R. Barton and S. Prabhakar, *J. Chem. Soc., Perkin Trans. 1*, 781 (1974).
(2) (a) S. Braverman and D. Segev, *J. Am. Chem. Soc.*, **98**, 1245 (1974); (b) G. Büchi and R. M. Freidinger, *ibid.*, **96**, 3332 (1974).
(3) (a) S. Braverman, *Int. J. Sulfur Chem., Part C*, **6**, 149 (1971); (b) S. Braverman and H. Mechoulam, *Isr. J. Chem.*, **5**, 71 (1967); (c) C. J. M. Stirling, *Chem. Commun*, 131 (1967); (d) G. Smith and C. J. M. Stirling, *J. Chem. Soc., C*, 1530 (1971); (e) S. Braverman and T. Globerman, *Tetrahedron*, **30**, 3873 (1974); (f) S. Braverman and H. Mechoulam, *ibid.*, **30**, 3883 (1974).
(4) For example, (a) B. M. Trost and R. La Rochelle, *Tetrahedron Lett.*, 3327 (1968); (b) J. F. Baldwin, R. E. Hackler, and D. P. Kelly, *Chem. Commun*, 537, 538, 1083 (1968); (c) P. A. Grieco, M. Meyers, and R. S. Finkelhor, *J. Org. Chem.*, **39**, 119 (1974).
(5) H. Kwart and T. J. George, *Chem. Commun*, 433 (1970).
(6) (a) T. Beetz and R. M. Kellogg, *J. Am. Chem. Soc.*, **95**, 7925 (1973); (b) T. Beetz and R. M. Kellogg, paper in preparation.
(7) Spectral data for **3**: ^{1}H NMR (CCl_4) δ 1.15 [s, 9, $(CH_3)_3C$–], 1.33 [s, 9, $(CH_3)_3C$–], 3.15 (dd, 2, J = 3.5, 2.4 Hz, $-CH_2-$),[8] and 5.06 (dd, 2, J = 3.5, 2.4 Hz, $-CH_2$); ir (KBr) 1335 and 1155 cm^{-1} (sulfur–oxygen bonds); uv (C_2H_5OH) λ_{max} 246 nm (ϵ 8750). In the coupled ^{13}C NMR spectrum there is seen in addition to the $(CH_3)_3C$– absorptions (relative to TMS) δ 158.1 (s, vinylidene C), 139.8 (s, vinylidene C), 132.7 (s, vinylidene C), 129.1 (s, vinylidene C), 68.2 (t, J_{CH} = 153 Hz, $-CH_2-$), and 36.5 (t, J_{CH} = 143 Hz, $-CH_2-$).
(8) Coupling constants confirmed by computer simulation [LAME: C. W. Haigh, *Annu. Rep. NMR Spectrosc.*, **4**, 311 (1971)].
(9) MULTAN computer program: G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr.*, **A27**, 368 (1971).
(10) Correct elemental analyses have been obtained for all new compounds save **4/5b,c**, which were too unstable for analysis, and **4/5d**. Spectral data were all in accord with the proposed structures. See also note concerning microfilm edition.
(11) Examples of this type of reaction are reported by (a) B. E. Kirk and D. R. Taylor, *J. Chem. Soc. Perkin Trans. 1*, 1844 (1974); (b) R. E. Banks, W. R. Deem, R. N. Hazeldine, and D. R. Taylor, *J. Chem. Soc., C*, 2051 (1966); (c) D. E. Applequist and J. D. Roberts, *J. Am. Chem. Soc.*, **78**, 4012 (1956); (d) Ya. M. Slobodin, Yu. A. Tallier, and I. Ismailova, *Zh. Org. Khim.*, **3**, 1529 (1967) (English translation, p 1484). (e) A failed attempt to realize this reaction has been reported by H. A. Staab and H-A. Kurmeier, *Chem. Ber.*, **101**, 2697 (1968). (f) The addition of benzyne to allenes could be considered a variant on this reaction: H. H. Wassermann and J. M. Fernandez, *J. Am. Chem. Soc.*, **90**, 5322 (1968); H. H. Wasserman and L. S. Keller, *Chem. Commun*, 1483 (1970). (g) For general references on allene cycloadditions, see J. E. Baldwin and R. H. Fleming, *Fortsch. Chem. Forsch.*, **15**, 281 (1970); D. Seebach, Houben-Weyl Methoden der Organischen Chemie, George Thieme Verlag, Stuttgart, 1971, IV/4, p 151 et seq.

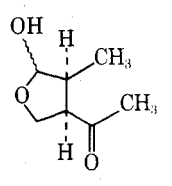
Department of Organic Chemistry **Tom Beetz**
Department of Structural Chemistry **Richard M. Kellogg***
University of Groningen, Zernikelaan **Conrad Th. Kiers**
Groningen, The Netherlands **Alie Piepenbroek**

Received September 2, 1975

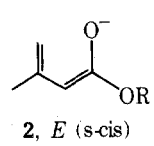
The Stereochemistry of Ester Dienolate Anions. A Stereoselective Route to Botryodiplodin

Summary: A three-step total synthesis of the antibiotic and antileukemic agent botryodiplodin by means of the stereoselective Claisen rearrangement of *cis*-crotyl senecioate is described.

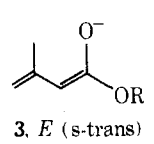
Sir: A short, stereoselective total synthesis of the antibiotic and antileukemic agent botryodiplodin[1,2] (**1**) has been achieved by a route which also provides evidence for the configuration of ester dienolate anions. Several recent re-



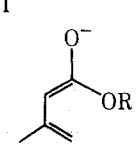
1



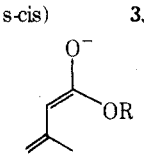
2, *E* (s-cis)



3, *E* (s-trans)

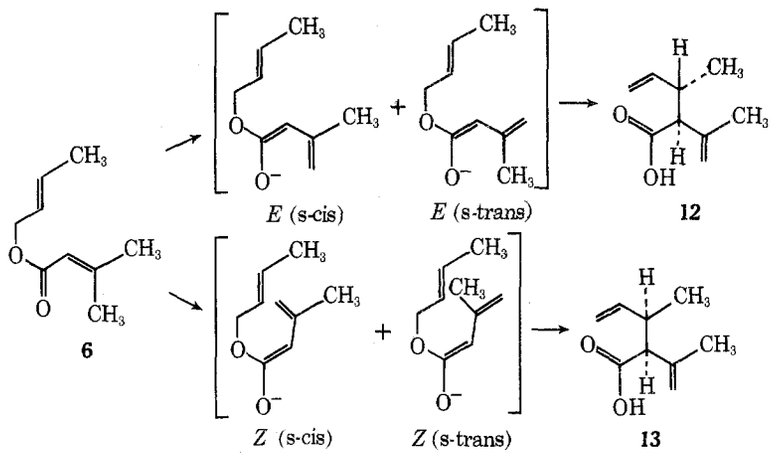


4, *Z* (s-cis)



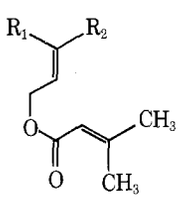
5, *Z* (s-trans)

Scheme I

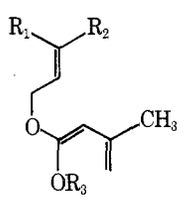


ports have appeared concerning the alkylation[3] or aldol condensation[4] of dienolate anions of α,β-unsaturated carboxylic acids or esters. These anions may adopt either *E* configuration **2** (s-cis) and **3** (s-trans) or *Z* configuration **4** (s-cis) and **5** (s-trans). It has been suggested[3c] that the dienolate **2** (R = Na) should be the most stable.

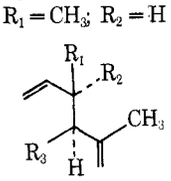
The recent extensions of the Claisen rearrangement to ester enolates,[5] and the high degree of stereoselectivity[6] well known in the vinyl ether Claisen rearrangement suggests that the rearrangement of *cis*- and *trans*-crotyl ester dienolate anions might be used as a probe to examine the initial stereochemistry of ester dienolates. Rearrangement of trans ester **6** (Scheme I) should give (2*S*),(3*S*)-acid **12**[7] via the *E* (s-cis or s-trans) dienolate anion or (2*S*),(3*R*)-acid **13** via the *Z* (s-cis or s-trans) dienolate. The opposite should hold true for the cis ester **7**.



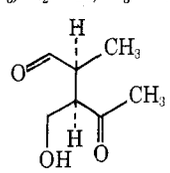
6, $R_1 = H$; $R_2 = CH_3$
7, $R_1 = CH_3$; $R_2 = H$



8, $R_1 = H$; $R_2 = CH_3$; $R_3 = TMS$
9, $R_1 = CH_3$; $R_2 = H$; $R_3 = TMS$



10, $R_1 = H$; $R_2 = CH_3$; $R_3 = CO_2TMS$
11, $R_1 = CH_3$; $R_2 = H$; $R_3 = CO_2TMS$
12, $R_1 = H$; $R_2 = CH_3$; $R_3 = CO_2H$
13, $R_1 = CH_3$; $R_2 = H$; $R_3 = CO_2H$
14, $R_1 = H$; $R_2 = CH_3$; $R_3 = CO_2CH_3$
15, $R_1 = CH_3$; $R_2 = H$; $R_3 = CO_2CH_3$
16, $R_1 = H$; $R_2 = CH_3$; $R_3 = CH_2OH$
17, $R_1 = CH_3$; $R_2 = H$; $R_3 = CH_2OH$



18

trans-Crotyl senecioate (**6**) and *cis*-crotyl senecioate (**7**) were prepared by standard methods. Treatment of **6** with lithium 2,2,6,6-tetramethylpiperidide[8] (THF, −78°, 15 min), followed by trimethylchlorosilane, gave silyl ketene acetal (**8**) which on heating to reflux rearranged to silyl ester **10**. This material hydrolyzed on work-up to the (2*S*),(3*S*)-acid **12**, in 95% overall yield (bp ~75° at 2.5 mm, mp 34–36°) (see Table I).[9,10] Similar treatment of the cis ester **7** gave (2*S*),(3*R*)-acid **13** in 88% yield (mp 29.5–31°).

The stereoselectivity[11] is 68% for the trans ester **6** and 82% for the cis ester. This is lower than the ~95% usually observed in the Claisen rearrangement and implies a 10–20% concentration of *Z* dienolate anion **4,5** with the *E* dienolate **2,3** predominating.[12]

Table I
Stereoselective Crotyl Senecioate Rearrangements

Ester	Conditions	Ratio[a] of 12:13	% yield[b]
6	LDA,[c] 25°	79:21	53
6	LiTMP,[d] −78°, TMSCl, Δ	84:16	95
7	LiTMP, −78°, TMSCl, Δ	9:91	88

[a] Ratios of isomers were determined by NMR integration of the methyl doublet (proton C, Table II) and by GLPC analysis of the methyl ester (CH_2N_2) on a 200-ft DB-TCP capillary column operating at 60°C. [b] Isolated yield of distilled or crystallized product. [c] Lithium diisopropyl amide. [d] Lithium 2,2,6,6-tetramethylpiperidide.

The reaction can be utilized for the construction of stereochemistry in acyclic systems such as botryodiplodin (**1**). Acid **13** was reduced with excess lithium aluminum hydride in ether to the alcohol **17** in 83% yield (bp 75° at 50 mm). Ozonolysis (O_3, CH_2Cl_2, −78°, Zn, AcOH) gave ketoaldehyde **18** which spontaneous cyclized to the lactol *dl*-botryodiplodin (**1**, 63%, bp ~130° at 5 mm). Spectral properties of *dl*-botryodiplodin and its acetate were identical with those reported by McCurry.[2a,b]

Acknowledgment. The authors gratefully acknowledge the generous support of the Indiana University Department of Chemistry and the Indiana University Research Funds.

Supplementary Material Available. Table II, containing 220-MHz PMR data for compounds **12–17** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St. N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-3309.

References and Notes

(1) R. S. Gupta, R. R. Chandran and P. V. Divekar, *Ind. J. Exp. Biol.*, **4**, 152 (1966); G. P. Arsenault and J. R. Althaus, *Chem. Commun.*, 1414 (1969).
(2) Recent syntheses of compound **1**: (a) P. M. McCurry, Jr., and K. Abe, *Tetrahedron Lett.*, 4103 (1973); (b) P. M. McCurry, Jr., and K. Abe, *J. Am. Chem. Soc.*, **95**, 5824 (1973); (c) T. Mukaiyama, M. Wada, and J. Hanna, *Chem. Lett.*, 1181 (1974).
(3) (a) M. W. Rathke and D. Sullivan, *Tetrahedron Lett.*, 4249 (1972); (b) J. L. Herrmann, G. R. Kieczykowski, and R. H. Schlelssinger, *Ibid.*, 2433 (1973); (c) G. Cainelli, G. Cardillo, M. Contento, and A. Umani-Ronchi,

Gazz. Chim. Ital., **104**, 625 (1974); (d) J. A. Katzenellenbogen and A. L. Crumrine, *J. Am. Chem. Soc.*, **96**, 5662 (1974); (e) J. A. Katzenellenbogen and A. L. Crumrine, 170th National Meeting of the American Chemical Society, Chicago, Ill., Aug 1975, abstracts, ORGN 24.
(4) C. A. Henrick, W. E. Willy, D. R. McKean, E. Baggiolini, and J. B. Siddall, *J. Org. Chem.*, **40**, 8 (1975), and references cited therein.
(5) S. Julia, M. Julia, and G. Linstrumelle, *Bull. Soc. Chim. Fr.*, 2693 (1964); M. Matsui and B. Stalla-Bourdillon, *Agr. Biol. Chem.*, **32**, 1246 (1968); R. T. Arnold and C. Hoffman, *Synth. Commun.*, **2**, 27 (1972); R. E. Ireland and R. H. Mueller, *J. Am. Chem. Soc.*, **94**, 5897 (1972); J. E. Baldwin and J. A. Walker, *Chem. Commun.*, 117 (1973); H. Kappeler, W. Wild, and J. Wild, U. S. Patent 3781333 (1973), *Chem. Abstr.*, **80**, 70996e (1973); J. A. Katzenellenbogen and K. J. Christy, *J. Org. Chem.*, **39**, 3315 (1974); G. Frater, *Helv. Chim. Acta*, **58**, 442 (1975).
(6) S. J. Rhoads and N. R. Raulins, *Org. React.*, **22**, 1 (1975).
(7) All new compounds reported in this paper are racemic but for convenience only one stereoisomer is drawn. Thus compound **12** is (2*S*),(3*S*) and (2*R*),(3*R*); compound **13** is (2*S*),(3*R*) and (2*R*),(3*S*).
(8) R. A. Olofson and C. M. Dougherty, *J. Am. Chem. Soc.*, **95**, 582 (1973).
(9) All new compounds possessed satisfactory analytical and spectral data. NMR spectral data for compounds **12–17** are collected in Table II (microfilm edition).
(10) Fractional crystallization of acids **12** and **13** substantially increased the purity of the major isomer. Care was taken, however, to assure that the isomer ratios in Table I were accurate by examination of the total crude product.
(11) Stereoselectivity is defined as (% major isomer − % minor isomer); see J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., 1971, p 10.
(12) An alternative explanation involves increased proportion of reaction proceeding via boat transition state.

Department of Chemistry
Indiana University
Bloomington, Indiana 47401

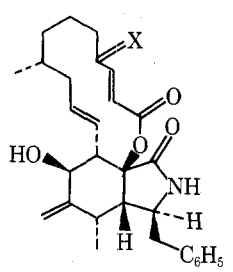
Stephen R. Wilson*
Richard S. Myers

Received August 19, 1975

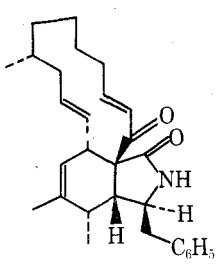
Synthesis of the Isoindolone Nucleus of the Cytochalasins

Summary: The isoindolone skeleton of the cytochalasins has been constructed stereospecifically via an intramolecular Diels–Alder reaction.

Sir: The cytochalasins are a group of microbial metabolites producing a variety of unusual biological effects upon living cells.[1] The members of this group of natural products are all characterized structurally by a saturated isoindolone skeleton fused to an 11- to 14-membered macrocyclic ring,[2-4] as shown in cytochalasins A (**1**), B (**2**), and proxiphomin



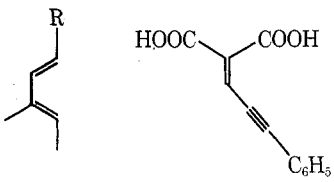
1, X = O
2, X = α-OH, β-H



3

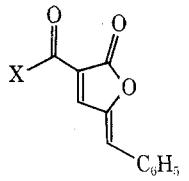
(**3**).[5] Although these compounds represent an exciting and difficult challenge for the synthetic chemist, to our knowledge no work has yet been reported in this area. We now wish to describe a stereospecific approach to the isoindolone nucleus of the cytochalasins.

Condensation of tiglic aldehyde with trimethyl phosphonoacetate (sodium hydride, benzene) produced methyl γ-methylsorbate (**4**) in 80% yield. Reduction of **4** to the alcohol **5**[6] [bp 40–45° (0.2 mm)] was effected in 87% yield with lithium aluminum hydride in ether. Diacid **6**, prepared as described[7] by condensation of malonic acid and phenyl propargaldehyde, was cyclized to the known butenolide **7**[8] by refluxing in *o*-dichlorobenzene. Compound **7** could be converted into the corresponding acid chloride **8** upon treatment with thionyl chloride in chloroform. The crude



4, R = $COOCH_3$
5, R = CH_2OH

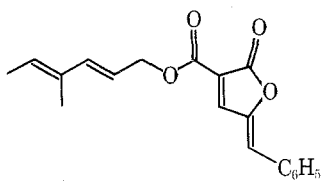
6



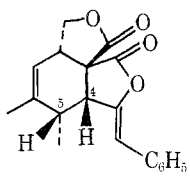
7, X = OH
8, X = Cl

acid chloride **8** was treated with a solution of alcohol **5** in pyridine at room temperature to produce the stable, crystalline ester **9** (80%), mp 106–108°.

Heating ester **9** in refluxing *o*-dichlorobenzene produced the crystalline tricyclic dilactone **10**: NMR ($CDCl_3$) δ 1.38

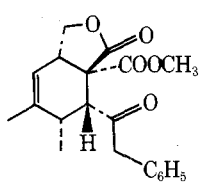


9

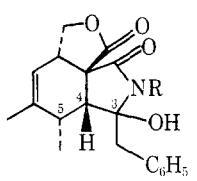


10

(3 H, d, J = 8 Hz), 1.80 (3 H, br s), 2.5 (1 H, m), 3.2 (1 H, m), 3.56 (1 H, d, J = 7 Hz), 4.65 (1 H, t, A of ABX), 5.25 (1 H, dd, B of ABX), 5.68 (1 H, s), 6.00 (1 H, m), 7.2–7.7 (5 H, m). One would expect that an endo transition state is preferred for this intramolecular Diels–Alder reaction,[9,10] thus producing the stereochemistry shown in structure **10**. The C-4–C-5 hydrogen coupling constant of 7 Hz in compound **10** supports assignment of a cis relationship to these protons.[11] Tricyclic lactone **10** was quite difficult to isolate because of its propensity for reaction with nucleophiles during chromatography. It was discovered that refluxing a methanolic solution of **10** led to formation of keto ester **11**:



11



12, R = H
13, R = $CH_2C_6H_5$

NMR ($CDCl_3$) δ 3.80 (3 H, s), 3.90 (2 H, s). The high reactivity of the butenolide ring of **10** toward nucleophiles was used in introducing nitrogen into the system.

Thus, on heating a dilute *o*-dichlorobenzene solution of ester **9** for 2.5 hr, followed by cooling in ice, and saturating with ammonia, crystalline tricyclic lactam **12** could be readily isolated (32% yield from **9**): mp 174–175°[12]; ir (film) 3400, 3300, 1750, 1710 cm^{-1}; NMR ($CDCl_3$) δ 3.1 (2 H, AB q, J = 14 Hz).

Similarly, treatment of the crude Diels–Alder product **10** with benzylamine produced lactam **13**[11,12] (36% frm **9**): ir ($CDCl_3$) 3350, 1740, 1700 cm^{-1}; m/e found 417.19520. Work is now in progress to utilize systems such as **12** and **13** in a total synthesis of the cytochalasins.

Acknowledgment. This research was supported by Grants HL 18450 and CA12568 from the National Institutes of Health and by Eli Lilly. We thank Mr. D. Kim for 100-MHz NMR spectra, Mr. R. Comi for preparation of intermediates, and Dr. C. E. Costello, MIT, for high resolution mass spectra.