and filtered through a short column of silica gel (2 g). Upon evaporation of the solvent, a yellow residue (25 mg) of 3-acetoxy-11-methoxy-18-norandrosta-3,5,8,11,13-pentaen-17-one was obtained: NMR δ 1.47 (s, 3 H), 2.17 (s, 3 H), 2.83 (m, 8 H), 3.43 (d, J = 4 Hz, 2 H), 3.92 (s, 3 H), 5.7 (t, J = 4 Hz, 1 H), 5.93 (br s, 1 H), 7.2 (s, 1 H); IR 1740, 1692, 1600 cm^{-1}; mass spectroscopic molecular weight 338.15163 (calcd for $C_{21}H_{22}O_4$ 338.15181).

Acknowledgments. This work was supported by the Contraceptive Development Branch, Center for Population Research, NICHD, NIH, under Contract NO1-HD-4-2831. We are grateful to Dr. Tanabe of SRI International, Menlo Park, Calif., for carrying out the androgen binding tests and to Professor John C. Sheehan for his encouragement of this work.

Registry No. **1b**, 5309-18-2; **2**, 22442-51-9; **3**, 22442-52-0; **4a**, 27230-52-0; **4b**, 27230-53-1; **5**, 70179-52-1; **6**, 27266-10-0; **7**, 70179-53-2; **8a**, 70179-54-3; **8b**, 70179-55-4; **10**, 70179-56-5; **11a**, 70179-57-6; **12**, 70179-58-7; **13**, 70179-59-8; acrylonitrile, 107-13-1; *N,N*-(diethylamino)-3-butanone, 3299-38-5; 3-acetoxy-11-methoxy-18-norandrosta-3,5,8,11,13-pentaen-17-one, 70179-60-1.

Stereoselective Synthesis of the Proposed American Coneflower Juvenile Hormone Mimic. Some Observations on the Cyclopropylcarbinyl Rearrangement in Substituted Systems

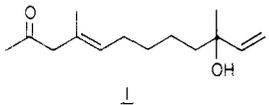
Manning P. Cooke, Jr.

Department of Chemistry, Washington State University, Pullman, Washington 99164

Received November 13, 1978

A stereoselective synthesis of the proposed structure (1) of echinolone, the potent juvenile hormone mimic from the American coneflower, is reported. Oxygen and trisubstituted olefin functionality were introduced through a cyclopropylcarbinyl rearrangement of carbinol **25**. The complexity of related rearrangements in model systems has been found to be a function of the presence or absence of remote unsaturation. Synthetic racemic 1 has been found to be devoid of JH activity in a standard assay, and these results are discussed with regard to the structure of the natural product.

Jacobson and co-workers have reported the isolation of a compound from the roots of *Echinacea angustifolia* D.C., the American coneflower, said to be a highly active juvenile hormone mimic.[1] The highly publicized mimic, dubbed "echinolone", reportedly produces marked juvenilizing effects in the standard *Tenebrio molitor* assay at levels below 1 μg. On the basis of spectral data,[2] microozonolysis, and carbon skeleton chromatography, the only structure for echinolone said to be consistent with these data is that of (+)-10-hydroxy-4,10-dimethyl-(*E*)-4,11-dodecadien-2-one (1). A nonstereoselective synthesis of 1 has recently been

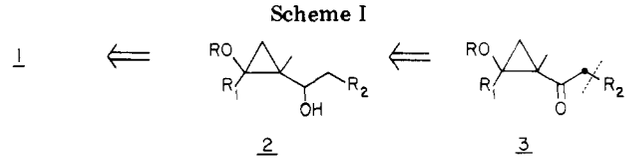


1

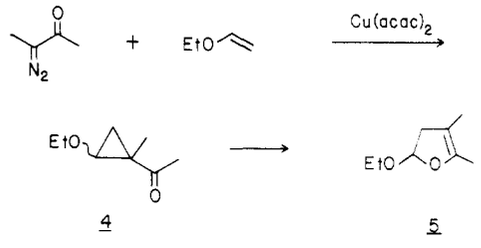
reported.[3] We report a stereoselective synthesis of racemic 1 resulting from our efforts to provide synthetic proof for the suggested structure of echinolone as well as some observations on the cyclopropylcarbinyl rearrangement used in its construction.

The key structural features in 1 which were considered in planning a synthesis were the presence of the β,γ-unsaturated carbonyl group at C-2, the proximal trisubstituted olefinic unit with its potential for isomerization, and the presence of the tertiary allylic alcohol containing the lone chiral center at C-10. We initially chose to attempt a synthesis of 1 through the use of a cyclopropylcarbinyl rearrangement of **2** (Scheme I) such that both the olefinic unit of correct stereochemistry and the proximal oxygen function could be introduced simultaneously at a late stage in the synthesis.

Scheme I



Scheme II



While the cyclopropylcarbinyl rearrangement[4] has found considerable use in the stereoselective synthesis of trisubstituted olefins,[5] more highly substituted systems

(1) (a) M. Jacobson, R. E. Redfern, and G. D. Mills, Jr., *Lloydia*, **38**, 473 (1975); (b) M. Jacobson, R. E. Redfern, and D. J. Voaden, Abstract no. PEST 73, 168th National Meeting of the American Chemical Society, Atlantic City, N.J., Sept 9–13, 1974; (c) *Chem. Eng. News*, **52**, 30 (September 23, 1974); (d) M. Jacobson, *Mitt. Schweiz. Entomol. Ges.*, **44**, 73 (1971).

(2) Only infrared spectral data has been published;[1a] mass and ^1H NMR spectral data are said to be consistent with the proposed structure, but no data has been disclosed. In addition microozonolysis is said to support structure 1 through formation of formaldehyde, 2,4-pentanedione, and 2-hydroxy-2-methylheptanal. Formation of the last product is clearly inconsistent with structure 1, however, though this may be the result of a typographical or transcriptional error.

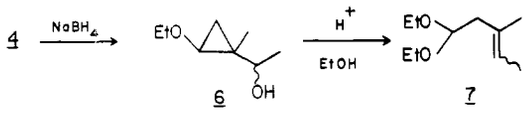
(3) O. P. Vig, S. D. Sharma, S. S. Bari, and V. K. Handa, *Indian J. Chem.*, **15B**, 1078 (1977).

(4) (a) K. L. Servis and J. D. Roberts, *J. Am. Chem. Soc.*, **86**, 3773 (1964); (b) Z. Majerski and P. V. R. Schleyer, *ibid.*, **93**, 665 (1971); (c) M. Julia, Y. Noël, and R. Guegan, *Bull. Soc. Chim. Fr.*, 3742 (1968); M. Julia and Y. Noël, *ibid.*, 3749 (1968); 3756 (1956); (d) S. Sarel, J. Yovell, and M. Sarel-Imber, *Angew. Chem., Int. Ed. Engl.*, **7**, 577 (1968); (e) K. S. Wiberg, B. A. Hess, Jr., and A. A. Ashe, III, in "Carbonium Ions", Vol. III, G. Olah and P. V. R. Schleyer, Eds., Wiley, New York, N.Y., 1973, p 1295.

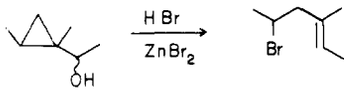
(5) (a) S. F. Brady, M. A. Ilton, and W. S. Johnson, *J. Am. Chem. Soc.*, **90**, 2882 (1968); (b) M. Julia, S. Julia, and R. Guêgan, *Bull. Soc. Chim. Fr.*, 1072 (1962); (c) D. J. Faulkner, *Synthesis*, 175 (1971); J. Reucroft and P. G. Sammes, *Q. Rev., Chem. Soc.*, **25**, 135 (1971).

0022-3263/79/1944-2461$01.00/0

Scheme III



Scheme IV

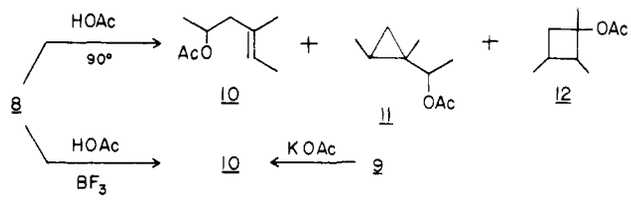


present new complications and have been less often employed.[6] An attractive feature of this approach was the possibility of introducing a large portion of the molecule (R_2 in **3**) through an alkylation of a simple cyclopropyl ketone. This approach also offered the possibility of deriving the alkylating agent from an optically active natural product such as linalool in the event that a synthesis of chiral **1** was desired. Such an approach would avoid difficulties anticipated in the generation or resolution of intermediates containing the allylic tertiary alcohol unit.

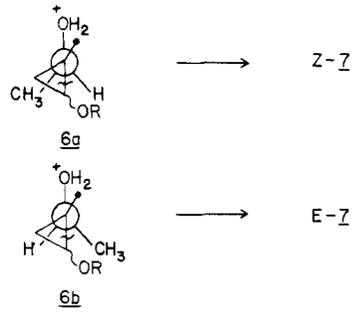
In order to investigate the feasibility of using an alkoxy-substituted cyclopropyl ketone such as **3** for direct introduction of the (*E*)-β,γ-unsaturated carbonyl unit in **1**, we attempted the preparation of the simple ketone **4** as shown in Scheme II. Decomposition of 3-diazo-2-butanone in the presence of ethyl vinyl ether under a variety of conditions gave complicated mixtures containing varying amounts of **4** which could be identified in NMR spectra by the presence of cyclopropyl resonances in the region δ 0–1.0 and by methyl singlets at δ 1.22 and 1.82 (methylcyclopropyl and acetyl resonances, respectively). Best results were obtained with hexane solutions and copper(II) acetylacetonate as catalyst; however, it soon became apparent that **4** was unstable—especially under acidic conditions. Reasonably pure **4** could be obtained by rapid distillation of the reaction mixture from Na_2CO_3 followed by preparative TLC on buffered (pH 8) plates. The ketone appeared to be a single isomer of undetermined stereochemistry by GLC and NMR spectral analysis. In any event, **4** readily rearranged to a mixture of volatile components which were not readily resolved. The appearance of vinyl methyl signals in the NMR spectra of aging solutions of **4** suggests that dihydrofuran **5** is the major rearrangement product. Mass spectral fragments of a small sample obtained by preparative GLC showed ions at 142 (M^+), 113 (M^+ – Et), and 97 (M^+ – OEt) further supporting this structure. Rearrangements of this type have been previously observed under more vigorous conditions.[7]

The reduction of freshly prepared **4** with sodium borohydride (Scheme III) gave somewhat more stable **6** as a 1:1 mixture of C-2 diastereomers, seen in NMR spectra as a pair of C-1 methyl doublets at δ 1.10 and 1.12. Treatment of ethanolic solutions of **6** with catalytic amounts of *p*-toluenesulfonic acid at 50 °C resulted in the rapid formation of **7** as an approximately equal mixture of geometrical isomers only partially resolvable by GLC but readily discernible by NMR analysis with the aid of

Scheme V



$Eu(fod)_3$ shift reagent. It seems likely that the diastereomers **6a** and **6b** give rise to *Z* and *E* olefins, respectively,



as a result of a concerted rearrangement in which the rupture of one of the cyclopropyl carbon–carbon bonds is greatly favored owing to the presence of the cation-stabilizing alkoxyl group.[8] This is in contrast to the behavior of unsubstituted systems where two equivalent cyclopropyl bonds are present and olefin stereochemistry is dictated by conformational effects.[5a] The considerable cation-stabilizing ability of the alkoxy group apparently allows little if any equilibration of the carbinol center (**6a** ⇌ **6b**) which would be expected to favor *E*-isomer formation through a more favorable rearrangement of **6b**. Indeed, when the rearrangement was monitored by GLC, a more rapid appearance of one of the olefin isomers (believed to be the *E* isomer on the basis of its longer retention time) was observed. It is interesting to note that substituted carbinol **8** has been found to rearrange to give predominantly the *E* isomer of **9** (Scheme IV). In this case the substituent, a methyl group, also dictates the direction of the cyclopropyl cleavage, but apparently the rearrangement is not a concerted process thereby allowing equilibration of the original carbinol center with subsequent rearrangement through the conformationally preferred diastereomer.[6d]

The instability of **4** and the apparent dependence of olefin stereochemistry upon relative carbinol configuration made this direct approach impractical. Insomuch as less activated carbinol **8** was found to rearrange in the desired manner under Johnson–Julia conditions[5a] (Scheme IV), it seemed that this system might be made to serve our purposes if conditions compatible with the allylic alcohol moiety in **1** could be found in which the homoallylic cation generated in the cyclopropylcarbinyl rearrangement was captured by an oxygen-containing nucleophile instead of bromide ion.[10] To this end we examined the acetolysis of model carbinol **8** under a variety of conditions to determine the feasibility of this modification. Solvolyses of **8** in acetic acid at 70–100 °C from 1 to 24 h (Scheme V) gave mixtures of acetates in which **10** was the major isomer along with **11** and a mixture of isomeric acetates thought to be **12** on the basis of NMR spectral analyses of the

(6) (a) M. Julia and G. LeThuillier, *Bull. Soc. Chim. Fr.*, 717 (1966); 728 (1966); M. Julia and M. Baillarge, *ibid.*, 734 (1966); (b) E. Wenkert, R. A. Mueller, E. J. Reardon, S. S. Sathe, D. J. Scharf, and G. Tosi, *J. Am. Chem. Soc.*, **92**, 7428 (1970); (c) E. J. Corey and P. Ulrich, *Tetrahedron Lett.*, 3685 (1975); (d) C. D. Poulter and C. J. Spillner, *J. Am. Chem. Soc.*, **96**, 7591 (1974).

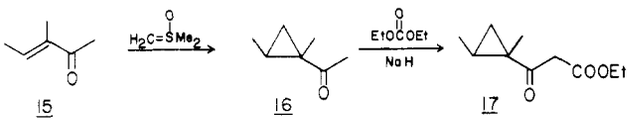
(7) D. E. McGreer and J. W. McKinley, *Can. J. Chem.*, **51**, 1487 (1973); A. Accary, Y. Infarnet, and J. Huet, *Bull. Soc. Chim. Fr.*, 2424 (1973).

(8) A similar phenomena has been observed in the solvolysis of diastereomeric methoxycyclopropylcarbinyl mesylates.[6c]

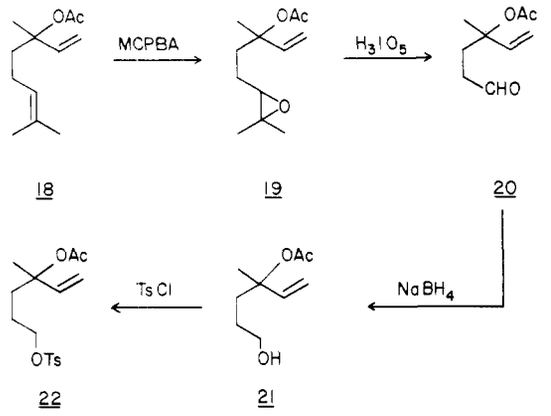
(9) M. P. Cooke, Jr., *Tetrahedron Lett.*, 1281 (1973).

(10) For simplicity we are assuming the involvement of discrete classical ions rather than the bridged or nonclassical ions which are likely involved.[4]

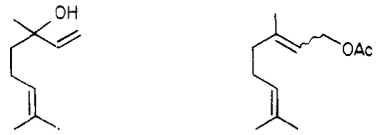
Scheme VI



Scheme VII



mixtures. Acetolysis of 8 in the presence of a catalytic amount of boron trifluoride etherate proceeded more rapidly, however, giving exclusively **10** in 1 h at 80 °C. In the presence of the acid catalyst, acetates **11** and **12** are apparently converted to the more stable acetate **10**. NMR spectral analysis with the aid of $Eu(fod)_3$ indicated **10** to be 82–89% *E* isomer.[11] Model studies with linalool (**13**)



and its acetate (**18**) indicated, however, that these conditions could not be tolerated by the tertiary allylic alcohol moiety present in **1**. Linalyl acetate (**18**) suffered total rearrangement to a mixture of isomeric acetates, identified by GLC analysis as **14**, upon standing at 25 °C for 1 h in acetic acid containing boron trifluoride etherate. Only 40% of linalool survived rearrangement under identical conditions. Acetolysis without added catalyst was more satisfactory in this regard with only 15% rearrangement of **13** being observed upon heating at 77 °C for 15 h. Under these same conditions, acetolysis of **8** gave 71% of the desired homoallylic acetate **10** and 21% of **12** by GLC analysis. Having demonstrated with this model system the feasibility of effecting the desired rearrangement, we prepared substituted cyclopropyl ketone **17** required for the synthesis of **1** as shown in Scheme VI.

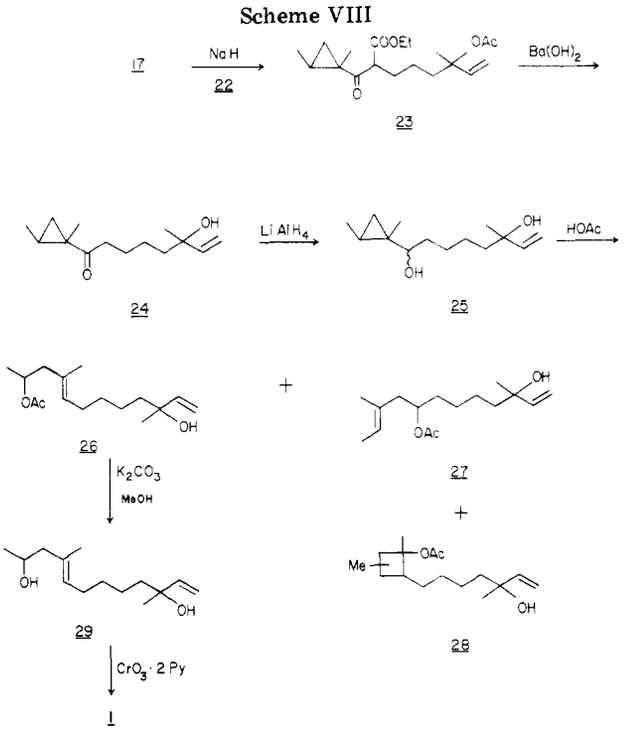
Cyclopropanation of **15** with dimethyloxosulfonium methylide by the literature procedure[12] gave **16** which was carbethoxylated with sodium hydride and diethyl carbonate to give keto ester **17** in 78% yield. The required alkylating agent for the elaboration of **17** was readily derived from racemic linalyl acetate (**18**) as shown in Scheme VII. Epoxidation of **18** with *m*-chloroperoxybenzoic acid gave epoxide **19** in 90% yield as a mixture of diastereomers. Direct cleavage of the epoxide with ethereal periodic acid by the method of Ireland[13] gave aldehyde **20**

(11) The same isomer was obtained upon treatment of **9** with KOAc in DMF.[5a]

(12) C. Agami and C. Prevost, *Bull. Soc. Chim. Fr.*, 2299 (1967).

(13) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley-Interscience, New York, N.Y., 1967, p 817.

Scheme VIII



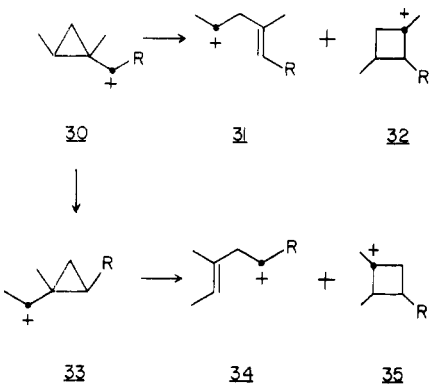
in 65% yield. Reduction of **20** with sodium borohydride gave, after purification by silica gel chromatography, alcohol **21** in 73% yield, which was converted into *p*-toluenesulfonate ester **22** in 80% yield by treatment with *p*-toluenesulfonyl chloride in pyridine.

Completion of the basic skeleton of **1** was accomplished as shown in Scheme VIII. Alkylation of the sodium salt from **17** and sodium hydride with sulfonate **22** in THF containing HMPA gave substituted keto ester **23**, which could be obtained in 68% yield following chromatography. Decarbethoxylation and acetate hydrolysis were effected by heating **23** with barium hydroxide in aqueous ethanol giving ketone **24** in 53% yield. Reduction of **24** with lithium aluminum hydride gave the desired diastereomeric diol **25** in nearly quantitative yield.

Optimum conditions for the rearrangement of **25** were found to be heating in acetic acid for approximately 7 h at 90 °C. Under these conditions solvolytic damage to the terminal tertiary alcohol was minimized with maximum formation of **26**. While desired homoallylic acetate **26** could be isolated from the mixture by careful multiple development preparative TLC, hydrolysis of the mixture allowed a more facile separation of the desired homoallylic alcohol **29**, which was obtained in 31% yield after chromatography. In addition to relatively small amounts of higher R_f diacetates resulting from combined cyclopropylcarbinyl and allylic alcohol rearrangement, shift reagent aided ^1H NMR spectral analysis of the acetolysis mixture indicated the presence of cyclobutyl acetates **28** as expected from the model studies with **8** (Scheme V). Unexpectedly, a significant amount of acetate **27** was also present (approximately 30%). This product is formally[10] a result of the formation of cation **33** (Scheme IX) resulting from a cyclopropyl–cyclopropyl rearrangement of **30** followed by collapse to homoallylic cation **34**. While products arising from this type of rearrangement are often observed in cyclopropylcarbinyl rearrangements,[14] products from this pathway were not detected in a previous synthesis[9] involving rearrangement of **37a** under John-

(14) E. C. Friedrich and J. D. Cooper, *Tetrahedron Lett.*, 4397 (1976), and references cited therein.

Scheme IX



Scheme X

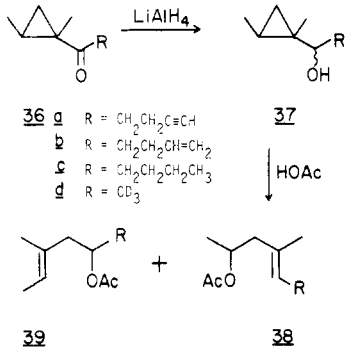


Table I. Acetolysis of 37 at 85 °C (1 h)

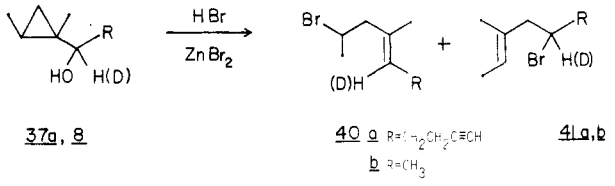
alcohol	38:39	(E)-38:(Z)-38
37a	88:12	96:4
37b	75:25	93:7
37c	66:34	88:12
37d	54:46	84:16

son–Julia conditions (HBr, $ZnBr_2$). This suggested that the extent of the cyclopropylcarbinyl–cyclopropylcarbinyl rearrangement (**30** → **33**) was a function of the substituent on the original carbinol center. To test this hypothesis, we prepared substituted cyclopropylcarbinols **37a–c** by the alkylation of **17** as in Scheme VIII by using substituents with varying degrees of terminal unsaturation. Indeed, different ratios of acetates **38** and **39** were observed as a function of side-chain unsaturation when **37** was heated in acetic acid containing boron trifluoride etherate added to ensure formation of only homoallylic products. Results of these model rearrangements are shown in Table I. Data were obtained by ^1H NMR spectral analysis of the mixture employing $Eu(fod)_3$ which allowed clean resolution of the acetate methyl signals of both **38** and **39** as well as signals associated with olefin configuration.[15] Only partial separations of mixtures could be obtained by GLC.

It is clear from Table I that the relative amounts of **39** arising from the cyclopropyl–cyclopropyl rearrangement (**30** → **33**) are a function of the structure of the carbinol substituent with increasing amounts of **39** being formed with increased side-chain saturation. While this mode of rearrangement was not visible in our original model study

(15) Small amounts of $Eu(fod)_3$ (Aldrich) were added directly to NMR tubes until satisfactory shifts were obtained. In all cases the acetate methyl resonance of (*E*)-**38** was shifted to lower fields than the acetate resonance of (*E*)-**39**. Acetate signals from *Z* isomers were always found at slightly higher field positions relative to their *E*-isomer counterparts. Graphical deconvolution of GLC chromatograms obtained at lower column temperatures gave estimated ratios of **38:39a–c** which were in agreement with the shift reagent aided NMR assignments used for the data reported in Table I.

Scheme XI



with **8** owing to the equivalency of the relevant ions **30** and **33** when R = CH_3, we were able to detect its presence through the solvolysis of deuterium-labeled alcohol **37d** prepared from **16** by deuterium exchange followed by $LiAlH_4$ reduction. ^1H NMR analysis with the aid of shift reagent again allowed determination of the ratio of **38** to **39**. It is clear that much of the undesired rearrangement to **33** also occurs in this simple system. It is also noteworthy that olefin stereoselectivity decreases with decreasing side-chain unsaturation with 16% *Z*-isomer formation being observed in **38d**.

The relative amounts of acetates **38** and **39** appear to be the result of a kinetically controlled process rather than a result of acetate equilibration. No significant change in the ratios of **38:39a–c** was observed upon increasing the reaction times from 1 to 8 h. Increased reaction times do lead to increasing amounts of (*Z*)-**38**, however. The *Z*-isomer content of **38a**, **38b**, and **38c** became 9, 18, and 28%, respectively, after a reaction time of 8 h. Thus significant additional olefin isomerization appears to occur under these conditions at longer reaction times. More significantly, multiple development preparative thick-layer chromatography (silica gel, 1:1 benzene–carbon tetrachloride, three developments) of the acetate mixture from **37c** gave enriched samples of **38c** and **39c** whose isomer ratios were unaltered upon reheating in the original reaction mixture for 2 h. It therefore appears that the ratio of acetates **38** and **39** is of kinetic origin and not the result of their equilibration.

In light of these results we were curious as to whether formation of isomeric products arising from the cyclopropyl–cyclopropyl rearrangement pathway were peculiar to our acetolysis conditions or whether they also occur under Johnson–Julia conditions with small amounts of isomeric homoallylic bromide having been overlooked in the previously reported rearrangement of **37a**. Indeed, careful GLC examination of the reaction mixture resulting from treatment of **37a** with HBr–$ZnBr_2$ (Scheme XI) showed the presence of a minor component, presumably **41a**, of slightly shorter retention time, which could not be completely resolved. The ratio of **40a** to **41a** was estimated to be 92:8 by graphical deconvolution. The bromide mixture could not be satisfactorily analyzed by ^1H NMR owing to the ineffectiveness of added shift reagent.

In two cases, however, we have examined the rearrangement by using deuterium-labeled substrates, thereby providing additional evidence that isomeric bromides are produced under Johnson–Julia conditions. Reduction of ketones **36a** and **16** with $LiAlD_4$ gave the corresponding carbinols, **37a**-d_1 and **8**-d_1, which were subjected to Johnson–Julia reaction conditions as shown in Scheme XI. Rearrangement of carbinol **37a**-d_1 would be expected to give homoallylic bromide **40a**-d_1 through ion **30** with deuterium being present at the vinyl carbon while the isomeric bromide **41a** arising through ion **33** via the cyclopropyl–cyclopropyl rearrangement would result in formation of **41a** with deuterium being present at the carbon bearing bromide. ^2H NMR spectral analysis showed **40a** and **41a** to be present in a ratio of approximately 93:7 which is in good agreement with the estimate

made by GLC analysis. A small amount of deuterium (13% of the total) was also found in an ^2H NMR peak corresponding to a vinyl methyl resonance and presumably arises through more subtle modes of deuterium scrambling. In the case of carbinol **8**, where extensive cyclopropyl–cyclopropyl rearrangement was inferred through the examination of **36d** in Scheme X, rearrangement of **8**-d_1 under Johnson–Julia conditions gave a single bromide (**40b** = **41b** when R = CH_3) whose ^2H NMR spectrum contained vinyl deuterium and >CDBr peaks in a ratio of 55:45 with 4% deuterium being present in a third peak corresponding to vinyl methyl incorporation. Thus comparable cyclopropyl–cyclopropyl rearrangement appears to occur under Johnson–Julia conditions as well.

Although we were able to obtain the desired homoallylic alcohol **29** required for our synthetic goal, it is noteworthy that the utility of the cyclopropylcarbinyl rearrangement in substituted systems of this type is clearly dependent on the nature of the substituents present.

The synthesis of racemic **1** was completed by oxidizing **29** with Collins' reagent[21] giving the desired ketone in 85% yield. The ketone was readily purified by preparative TLC followed by bulb-to-bulb distillation. Product structure is supported by both combustion and spectral data. The ^1H NMR spectrum of the synthetic ketone shows a single C-1 acetyl methyl resonance at δ 2.07 and a single C-3 methylene resonance at δ 3.00 as well as the expected 4-methyl broadened singlet and C-5 vinyl hydrogen triplet at δ 1.60 and 5.32, respectively. The presence of an IR band at 1711 cm^{-1} supports the presence of the unconjugated carbonyl group at C-12.[16] The presence of undesired *Z* isomer could not be detected by Eu(fod)$_3$-aided NMR analysis of this sample, suggesting its removal during the two chromatographic separations following rearrangement of **25**. A small amount of *Z*-isomer formation would be expected in light of the model studies in Table I.

Unfortunately, we have not been able to confirm that **1** is the natural product echinolone reported by Jacobson. Refusal by the author to provide a sample of the natural product for comparison has frustrated attempts to verify the identity of our synthetic material with the natural product in the conventional manner. Vig has noted a similar inability to obtain data bearing on this structure.[3] We have determined, however, that our synthetic racemic **1** is totally devoid of juvenile hormone activity in the standard *Tenebrio* assay used by Jacobson.[17] Interestingly, Vig has reported that his synthetic racemic material does give JH activity with a different insect, *Dysdercus koenigu* (F), the common Indian red cotton bug. We have been unable to obtain any details or a sample for comparison from Vig, however, Thus, either the structure (**1**) assigned to echinolone is incorrect but fortuitously possesses JH activity in this particular insect or the structure of echinolone is indeed that represented by **1** and the racemic material is biologically inactive in *Tenebrio*. The latter possibility is quite intriguing in that it requires inhibition of activity by the unnatural levorotatory isomer. To our knowledge no such inhibition of JH action has been reported. An example of enantiomeric inhibition of pheromone action has been reported recently.[18]

Finally, an attempt has been made to establish the relationship of **1** to "echinolone" by independent isolation of the natural product. A sample of American coneflower roots[19] was continuously extracted with pentane, and the extracts were carefully examined chromatographically for the presence of a component corresponding to synthetic **1**. We were unable to detect the presence of **1** in our extracts by comparative TLC, and the appropriate chromatographic zone was devoid of any JH activity in the standard *Tenebrio* assay performed in our laboratory. A different zone did show feeble activity but could not be further resolved. The low level of this activity makes this finding of questionable significance. Such negative evidence is not conclusive, however, in that our plant samples were of a different origin than those used in Jacobson's studies.

In the absence of an authentic sample of "echinolone" this question can only be resolved by the synthesis of optically active **1**. This should be possible with our approach and chiral linalyl acetate.

Experimental Section

General Procedures. Infrared spectra were recorded as films (neat) or as solutions (CCl_4, 0.1-mm path) by using a Beckman IR-18A spectrophotometer. ^1H NMR spectra were recorded with a Varian EM 360 spectrometer using solutions in the solvents indicated with Me_4Si as an internal standard. ^2H NMR spectra were recorded at 13.82 MHz by using a Bruker WH-90 spectrometer. Mass spectral data were obtained with a Varian M-66 mass spectrometer at 75 eV. GLC analyses were carried out with a Hewlett-Packard 700 gas chromatograph using 6 ft × 0.25 in. columns of (A) 10% UCW-98 or (B) 10% Carbowax, both on 80/100 mesh acid-washed Chromosorb W swept with helium carrier gas at 60 cm^3/min at the column temperatures indicated. TLC was performed by using Merck silica gel-60 F-254 plates. Preparative thick-layer chromatography (PTLC) was performed on 20 × 20 cm plates coated with a 1–2-mm layer of Merck silica gel-60 PF-254. Baker 60–200 mesh silica powder was used for column chromatography. Bulb-to-bulb distillations of the Kugelrohr type were conducted at the air oven temperatures and pressures cited. Analyses were performed by the analytical service of the University of Idaho.

3-Acetoxy-6,7-epoxy-3,7-dimethyl-1-octene (19). A mechanically stirred solution containing 39.2 g (0.2 mol) of (±)-linalyl acetate in 500 mL of methylene chloride was cooled by means of an ice bath. To this solution was added over 10 min a solution containing 40.6 g (0.2 mL) of 85% *m*-chloroperoxybenzoic acid (MCPBA) in 250 mL of methylene chloride. The mixture was stirred at 5 °C for 0.5 h and then treated with small portions of MCPBA (approximately 6 g) until further portions were not consumed (starch–iodide paper) and the starting material disappeared (GLC, column A, 150 °C). The mixture was filtered and the solution phase was washed sequentially with aqueous $NaHCO_3$, water, and brine and dried (Na_2SO_4). Solvent removal under reduced pressure gave an oil which upon distillation gave 38 g (90%) of **19** as a 1:1 mixture of diastereomers: bp 80 °C (0.8 mm) (lit.[20] bp 130 °C (20 mm)); IR (neat) 1737, 1370, 1250 cm^{-1}; NMR (CCl_4) δ 1.18, 1.22 (s, 6 H, $OC(CH_3)_2$), 1.25–2.13 (m, 4 H, methylene), 1.48, 1.52 (s, 3 H, CH_3COAc, two diastereomers), 1.93 (s, 3 H, OAc), 2.52 (t, 1 H, J = 6.4 Hz, HCO), vinyl ABX 5.10 (dd, H_A), 5.05 (dd, H_B), 5.90, and 5.97 (2 dd, H_X, two diastereomers, J_{AB} = 1.8 Hz, J_{AX} = 18 Hz, J_{BX} = 10 Hz).

4-Acetoxy-4-methyl-5-hexenal (20). To a solution of 12.7 g (0.06 mol) of **19** in 1 L of anhydrous ether was added portionwise 15.0 g (0.066 mol) of powdered periodic acid over 20 min with vigorous mechanical stirring.[13] The mixture was stirred 0.5 h whereupon the ether layer was decanted from the insoluble iodic acid and washed three times with water, once with dilute $NaHCO_3$ solution followed by water, and once with brine. The solution was dried (Na_2SO_4) and concentrated under reduced pressure.

(16) The IR spectrum of our synthetic racemic sample corresponds closely with the data reported by Vig[3] and Jacobson.[1a]

(17) Assays were performed both in our laboratory and by Zoecon Corp.

(18) J. H. Tumlison, M. G. Klein, R. E. Doolittle, T. L. Ladd, and A. T. Proveaux, *Science*, **197**, 789 (1977).

(19) Whole dried roots of *Echinacea angustifolia* D.C. were obtained from World Wide Herbs, Ltd.

(20) M. Mousseron-Canet and C. Levallois, *Bull. Soc. Chim. Fr.*, 993 (1963).

Distillation of the residual oil gave 6.62 g (65%) of pure **20**: bp 73–75 °C (2 mm); IR (neat) 2840, 2738, 1738, 1730, 1252 cm^{-1}; NMR (CCl_4) δ 1.53 (s, 3 H, CH_3), 1.94 (s, 3 H, CH_3COO), 2.0–2.6 (m, 4 H, methylene), vinyl ABX 5.12 (dd, H_A), 5.08 (dd, H_B), 5.92 (dd, H_X, J_{AB} = 1.6 Hz, J_{AX} = 18 Hz, J_{BX} = 10 Hz), and 9.90 (t, 1 H, J = 1.5 Hz, CHO).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.70; H, 8.29.

4-Acetoxy-4-methyl-5-hexen-1-ol (21). A solution containing 0.76 g (0.02 mol) of sodium borohydride in 40 mL of methanol was prepared at 0–5 °C and immediately 5.45 g (0.032 mmol) of **20** was added dropwise with stirring. After 10 min excess hydride was destroyed by the dropwise addition of 2 mL of acetaldehyde, and the mixture was diluted with 300 mL of water and extracted twice with ether. The dried extracts (Na_2SO_4) gave, after concentration under reduced pressure, crude **21**, which was purified by column chromatography on silica gel. Elution with 5:1 methylene chloride–ethyl acetate gave 4.0 g (73%) of nearly pure **21** as an oil which was used for subsequent reactions: NMR (CCl_4) δ 1.50 (s, 3 H, CH_3), 1.1–2.1 (m, 4 H, methylene), 1.95 (s, 3 H, CH_3COO), 3.37 (s, 1 H, OH), 3.48 (t, 2 H, J = 6.5 Hz, CH_2OH), vinyl ABX 5.09 (dd, H_A), 5.04 (dd, H_B), 5.95 (dd, H_X, J_{AB} = 1.8 Hz, J_{AX} = 18 Hz, J_{BX} = 10 Hz). Attempted distillation resulted in partial decomposition. An analytical sample was obtained as the *p*-nitrobenzoate ester, which was obtained pure after silica gel chromatography followed by bulb-to-bulb distillation at 120 °C (0.1 mm).

Anal. Calcd for $C_{16}H_{19}NO_6$: C, 59.81; H, 5.96; N, 4.36. Found: C, 60.07; H, 6.02; N, 4.13.

4-Acetoxy-4-methyl-5-hexenyl *p*-Toluenesulfonate (22). A solution of 810 mg (4.7 mmol) of **5** in 3.0 mL of dry pyridine was stirred at 0 °C, and 980 mg (5.1 mmol) of *p*-toluenesulfonyl chloride was added in small portions over 5 min. The mixture was stirred at 0–10 °C for 4 h and then treated dropwise with 1 mL of water followed by 20 mL of water. Extraction with ether gave, after drying (Na_2SO_4) and solvent removal, **22** as an oil which was further dried by concentration of a benzene solution under reduced pressure followed by storage at 0.1 mm for 1 h. In this way **22** was obtained as an oil, 1.23 g (80%), which was used directly without further purification: NMR (CCl_4) δ 1.45 (s, 3 H, CH_3), 1.5–1.8 (bm, 4 H, methylene), 1.90 (s, 3 H, OAc), 2.42 (s, 3 H, $ArCH_3$), 3.93 (t, 2 H, J = 5.7 Hz, CH_2OTs), vinyl ABX 5.03 (dd, H_A), 5.00 (dd, H_B), 5.88 (dd, H_X, J_{AB} = 1.8 Hz, J_{AX} = 18 Hz, J_{BX} = 10 Hz), and 7.2–7.8 (m, 4 H, Ar).

Ethyl 3-(*cis*-1,2-Dimethylcyclopropyl)-3-oxopropanoate (17). Sodium hydride, 7.70 g (160 mmol) of a 50% mineral oil dispersion, was placed in a 500-mL flask under dry nitrogen and freed of mineral oil by three successive treatments with 50 mL of dry pentane, which after brief stirring was removed by decantation. To the oil-free sodium hydride was added 40 mL of dry diethyl carbonate followed by 7.87 g (70 mmol) of 1-acetyl-*cis*-1,2-dimethylcyclopropane[12] and 10 drops of absolute ethanol. The mixture was heated in an oil bath (100–110 °C) with stirring until the vigorous exothermic reaction commenced whereupon heating was discontinued and the mixture was allowed to reflux until the reaction and hydrogen evolution subsided. The mixture was then heated at 100 °C with stirring for one additional hour and then cooled. Excess diethyl carbonate was removed under reduced pressure. The residue was treated with 200 mL of ether and, with stirring, there was added 11 mL of acetic acid over several min. The ethereal solution was washed sequentially with several portions of water, dilute $NaHCO_3$ solution, and brine and dried over Na_2SO_4. Distillation gave 10.0 g (78%) of pure **17**: bp 105 °C (5 mm); IR (neat) 1740 (COOEt), 1687 cm^{-1} (Cp–C=O); NMR (CCl_4) δ 0.2–1.5 (m, 3 H, Cp), 1.10–1.18 (bm, 3 H, 2-Me), 1.25 (t, 3 H, J = 7 Hz, CH_3CH_2O), 1.32 (s, 3 H, 1-Me), 3.33 (s, 2 H, $COCH_2COOR$), 4.12 (q, 2 H, J = 7 Hz, CH_3CH_2O).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.00; H, 8.81.

8-(*cis*-1,2-Dimethylcyclopropyl)-3-methyl-8-oxo-1-octen-3-ol (24). To a slurry of 8.5 mmol of oil-free sodium hydride in 20 mL of dry THF was added 1.48 g (8.0 mmol) of **17**. The mixture was stirred until homogeneous (approximately 0.3 h) whereupon 2.80 g (8.6 mmol) of **22** in 10 mL of THF was added followed by 2.6 mL of hexamethylphosphoric triamide. The mixture was stirred at 55 °C for 36 h, cooled, and made slightly acidic by the dropwise addition of acetic acid. Volatiles were removed under reduced pressure and the residue was treated with water and extracted with ether. The usual workup gave an oil which was purified by column chromatography. Elution with methylene chloride to remove starting materials followed by 5:1 methylene chloride–ethyl acetate gave keto ester **23** as an oil (2.3 g, 85%) which was hydrolyzed directly without further purification. The above keto ester in 6 mL of ethanol was added to a mixture containing 4.7 g (15 mmol) of $Ba(OH)_2 \cdot 8H_2O$ in 13 mL of water. The mixture was heated under nitrogen at reflux for 20 h and then concentrated by allowing ethanol to distill from the reaction flask. Water (20 mL) was added and then decanted from solids and extracted with ether. The remaining solids were likewise extracted with ether, and the original aqueous phase was acidified at 5 °C to pH 3 with concentrated hydrochloric acid and extracted again with ether. The combined ether extracts were washed with portions of water, dilute $NaHCO_3$, water, and brine and dried over Na_2SO_4. Solvent removal gave crude **24** which was purified by column chromatography (silica gel, methylene chloride–ethyl acetate). Bulb-to-bulb distillation (150 °C (0.1 mm)) gave 0.81 g (53%) of pure **24**: IR (neat) 3460 (OH), 1680 cm^{-1} (CO); NMR (CCl_4) δ 0.2–1.3 (m, 3 H, Cp), 1.15 (m, 3 H, 2-MeCp), 1.20 (s, 3 H, $OCCH_3$), 1.30 (s, 3 H, 1-MeCp), 1.12–1.16 (bm, 6 H, methylene), 2.37 (m, 2 H, CH_2CO), vinyl ABX 5.13 (dd, H_A), 4.95 (dd, H_B), and 5.88 (dd, H_X, J_{AX} = 17.6 Hz, J_{BX} = 10.5 Hz, J_{AB} = 2.1 Hz).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.63; H, 10.76.

8-(*cis*-1,2-Dimethylcyclopropyl)-3-methyl-1-octene-3,8-diol (25). A solution of 180 mg (0.8 mmol) of **24** in 1.0 mL of anhydrous ether was added dropwise with stirring at 0 °C to 6 mL of ether containing 0.25 mL of 2.5 M $LiAlH_4$ in THF. The mixture was stirred for 0.5 h whereupon water was added dropwise to destroy excess hydride followed by several drops of 4 N NaOH to granulate the aluminum residue. Filtration and evaporation of the dried ether solution (Na_2SO_4) gave 175 mg (95%) of **25** which was homogeneous by TLC analysis (silica gel, 5:1 methylene chloride–ethyl acetate). An analytical sample was obtained by bulb-to-bulb distillation (130 °C (0.03 mm)): IR (CCl_4) 3600, 3380 (b, OH) cm^{-1}; NMR (CCl_4) δ –0.3–1.2 (m, 3 H, Cp), 0.98 (s, 3 H, 1-CH_3Cp), 1.07 (d, 3 H, J = 5 Hz, 2-MeCp), 1.22 (s, 3 H, $OCCH_3$), 1.38 (b, 8 H, methylene), 2.3–2.8 (bm, 3 H, CHOH, OH), vinyl ABX 5.20 (dd, H_A), 5.00 (dd, HB), and 5.95 (dd, H_X, J_{AX} = 17.6 Hz, J_{BX} = 10 Hz, J_{AB} = 2 Hz).

Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 74.05; H, 11.31.

3,9-Dimethyl-(*E*)-1,8-dodecadiene-3,11-diol (29). A solution of 155 mg (0.70 mmol) of **25** in 5 mL of glacial acetic acid was heated at 90 °C for 7.8 h. The cooled solution was diluted with water and extracted three times with pentane. The dried pentane extracts gave 175 mg of crude acetates. The minor amount of diacetates (R_f 0.7) were separated from monoacetates (R_f 0.5) by PTLC (silica gel, 5:1 methylene chloride–ethyl acetate). The monoacetates (97 mg) could be chromatographically resolved (TLC) by repeated development (3:1 hexane–ether, three times) but were directly hydrolyzed to the more easily purified alcohols by stirring with 1.5 mL of absolute methanol containing 250 mg of anhydrous K_2CO_3 for 1.5 h at 25 °C. Dilution with water and extraction with ether gave diols which upon PTLC (3:2 ether–hexane, two developments) gave 48 mg (31%) of **29** (TLC, 3:1 methylene chloride–ethyl acetate, two times, R_f 0.33) and small amounts of other diols (R_f 0.14–0.25). An analytical sample of **29** was obtained by bulb-to-bulb distillation at 140 °C (0.03 mm): IR (CCl_4) 3600, 3360 (OH), 2960, 2920, 2855, 1635 (C=C), 1450, 1370, 1260, 1110, 995, 925 cm^{-1}; NMR (CCl_4) δ 1.13 (d, 3 H, J = 6 Hz, CH_3CHO), 1.23 (s, 3 H, CH_3CO), 1.30–1.57 (b, 6 H, methylene), 1.65 (bs, 3 H, vinyl CH_3), 1.85–2.35 (m, 6 H, allylic and OH), 3.90 (m, 1 H, CHO), vinyl ABX 5.25 (dd, H_A), 5.07 (dd, H_B), 6.00 (dd, H_X, J_{AX} = 17.6 Hz, J_{BX} = 10.8 Hz, J_{AB} = 2.0 Hz), and 5.30 (m, 1 H, vinyl).

Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 74.10; H, 11.44.

(±)-10-Hydroxy-4,10-dimethyl-(*E*)-4,11-dodecadien-2-one (1). A solution of Collins' reagent was prepared from 6.0 g of CrO_3, 9.65 mL of pyridine, and 150 mL of methylene chloride as described.[21] A 15-mL portion of this solution was found to oxidize

1.0 mmol of alcohol. A solution containing 27 mg (0.12 mmol) of **29** in 1.0 mL of dry methylene chloride was stirred at 0 °C and treated with 3.0 mL of Collins' reagent solution. The mixture was stirred *6.0* min and then treated with 200 μL of ethanol to consume excess oxidant and stirred at 0 °C for 10 min. The solution phase was decanted from the salts which separated and the residue was extracted with a small amount of pentane. The combined extracts were filtered and concentrated under reduced pressure at a temperature not exceeding 20 °C. The resulting oil was dissolved in a small amount of pentane and filtered, and the solvent was again removed under reduced pressure. Purification by PTLC (3:1 methylene chloride–ethyl acetate, R_f 0.5) gave 23 mg (85%) of 1 rendered solvent free by bulb-to-bulb distillation at 150 °C (<0.2 mm): IR (neat) 3450, 3080, 2930, 2860, 1711 (CO), 1640 (w), 1455, 1360, 1238, 1160, 1000, 922, 690 cm^{-1}; NMR (CCl_4) δ 1.22 (s, 3 H, CH_3CO), 1.07–2.10 (bm, 8 H, methylene), 1.60 (bs, 3 H, vinyl CH_3), 2.07 (s, 3 H, CH_3CO), 3.00 (bs, 2 H, CH_2CO), vinyl ABX 5.22 (dd, H_A), 5.03 (dd, H_B), 5.97 (dd, H_X, J_{AX} = 18 Hz, J_{BX} = 10 Hz, J_{AB} = 2 Hz), and 5.32 (t, 1 H, J = 7 Hz, vinyl).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.96; H, 10.53.

1-(2-Ethoxy-1-methylcyclopropyl)ethanol (6). To a slurry of 1.5 g of active manganese dioxide[22] in 10 mL of methylene chloride was added 0.5 g (5 mmol) of biacetyl hydrazone.[23] The mixture was stirred for 1 h and the manganese dioxide was removed by filtration. Solvent removal under reduced pressure (40 °C (15 mm)) gave 3-diazo-2-butanone[24] as a yellow oil used without further purification. The diazo ketone was dissolved in 18 mL of hexane containing 4 mL of freshly distilled ethyl vinyl ether and 300 mg of copper(II) acetylacetonate. The mixture was heated overnight in an oil bath maintained at 65 °C. The residue obtained after filtration and solvent removal under reduced pressure was subjected to rapid bulb-to-bulb distillation (150 °C (50 mm)) and the oil so obtained (crude **4**) was quickly reduced by addition to a solution of 200 mg of sodium borohydride in 3 mL of a 1:1 mixture of methanol–water containing a small pellet of potassium hydroxide. The mixture was stirred 20 min at 20 °C and then treated with a small volume of acetone to consume the excess hydride. Solvent removal under reduced pressure followed by extraction with ether gave crude **6** which was purified by PTLC (silica gel, 1:1 ether–hexane, two developments). Further purification by bulb-to-bulb distillation (150 °C (40 mm)) gave approximately 200 mg (28%) of **6**: NMR (CCl_4) δ 0.1–0.9 (m, 2 H, cyclopropyl), 1.07 (s, 3 H, CH_3C), 1.12 (d, 3 H, J = 6.5 Hz, CH_3), 1.67 (t, 3 H, CH_3CH_2O), 2.85–3.22 (m, 1 H, EtOCH), 3.50 and 3.53 (2 q, 2 H, CH_2O, two diastereomers).

Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.57; H, 11.28.

Ethanolysis of 6. To a solution containing 145 mg of **6** in 3 mL of absolute ethanol was added 30 μL of a solution containing 5 mg of *p*-toluenesulfonic acid hydrate in 0.5 mL of ethanol. The solution was heated at 50 °C for 4 min, cooled, poured into water, and extracted with pentane. Solvent removal gave **7** as an oil purified by bulb-to-bulb distillation (110 °C (90 mm)). The mixture of isomers could be partially resolved by GLC (column B, 95 °C): NMR (CCl_4) δ 1.67 (t, 6 H, CH_3CH_2O), 1.5–1.8 (b, 6 H, vinyl methyls), 2.27 (bt, 2 H, allylic), 3.3–3.8 (m, 2 H, CH_2O), 4.53 (t, 1 H, $(EtO)_2CH$), 5.33 (bq, 1 H, vinyl).

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.84; H, 11.97.

1-(*cis*-1,2-Dimethylcyclopropyl)ethanol (8). A solution of 2.10 g (55 mmol) of sodium borohydride in 60 mL of water was treated with a small pellet of sodium hydroxide and 20 mL of methanol. To this solution was added, with stirring, 7.80 g (70 mmol) of **16**[12] over 2 min. The mixture was stirred vigorously for 5 h and then extracted repeatedly with pentane. The dried extracts (Na_2SO_4) gave, after distillation, pure **8**: 5.6 g (72%); bp 148–152 °C; IR (neat) 3400, 3060, 2980, 1452, 1380, 1111, 1100, 1070 cm^{-1}; NMR (CCl_4) δ −0.25–0.80 (m, 3 H, cyclopropyl), 0.98 (s, 3 H, CH_3C), 1.00 (d, 3 H, CH_3CH), 1.10, 1.12 (2 d, 3 H, J = 6.4 Hz, CH_3CHOH, two diastereomers), 2.90 and 2.97 (2 d, 1 H, J = 6.4 Hz, O-CH, two diastereomers).

Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.62; H, 12.40.

4-Methyl-(*E*)-4-hexen-2-ol Acetate (10). A solution containing 200 mg (1.75 mmol) of **8**, 6 mL of glacial acetic acid, and a drop of boron trifluoride etherate was heated at 80 °C for 1 h, cooled, poured into water, and extracted with pentane. The pentane layer was washed with water and dilute sodium bicarbonate and dried over sodium sulfate. Bulb-to-bulb distillation (110 °C (150 mm)) of the oil obtained after concentration gave 215 mg (78%) of **10**, pure by GLC analysis (column B, 110 °C): IR (neat) 1740, 1240 cm^{-1}; NMR (CCl_4) δ 1.15 (d, 3 H, J = 6 Hz, CH_3CHOAc), 1.5–1.7 (d, s, 6 H, vinyl methyls), 1.97 (s, 3 H, OAc), 2.0–2.4 (m, 2 H, allylic CH_2), 5.06 (m, 1 H, AcOCH), 5.30 (qt, 1 H, vinyl). The addition of $Eu(fod)_3$ produced a 0.33-ppm separation of the acetyl resonances of the *E* and *Z* isomers present in a ratio 5.14:1 (84% *E*).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.26; H, 10.25.

Preparation of ketones 36a–c. Ketones were prepared by using the procedure described above for the preparation of **24** through the alkylation of **17** with propargyl bromide, allyl bromide, and propyl iodide, respectively, followed by hydrolysis with barium hydroxide.

36a: bp 105 °C (17 mm); 45%; IR (neat) 3300, 2127, 1690 cm^{-1}; NMR (CCl_4) δ 0.2–1.2 (m, 3 H, cyclopropyl), 1.1–1.2 (m, 3 H, CH_3CH), 1.33 (s, 3 H, CH_3C), 1.80 (t, 1 H, J = 2.3 Hz, C≡CH), 2.0–2.8 (m, 4 H, methylene).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.37. Found: C, 79.91; H, 9.64.

36b: bulb-to-bulb distillation at 170 °C (17 mm); IR (neat) 1688, 1640 cm^{-1}; NMR (CCl_4) δ 0.1–1.2 (m, 3 H, cyclopropyl), 1.13 (d, 3 H, CH_3CH), 1.33 (s, 3 H, CH_3C), 2.0–2.7 (m, 4 H, CH_2CH_2), 4.8–5.2 (m, 2 H, C=CH_2), 5.4–6.2 (m, 1 H, CH=C).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.80; H, 10.99.

36c: bulb-to-bulb distillation at 160 °C (17 mm); IR (neat) 1690 cm^{-1}; NMR (CCl_4) δ 0.2–1.2 (m, 3 H, cyclopropyl), 0.92 (t, 3 H, J = 6 Hz, CH_3CH_2), 1.07–1.17 (m, 3 H, CH_3CH), 1.32 (s, 3 H, CH_3C), 1.1–1.7 (m, 4 H, CH_2CH_2), 2.37 (t, 2 H, CH_2CO).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.89; H, 11.76. Found: C, 77.82; H, 12.01.

1-(*cis*-1,2-Dimethylcyclopropyl)ethanol-*2*-d_3 (37d). Methyl ketone **16**, 1.0 g, was stirred at 80 °C with 8 mL of D_2O containing 100 mg of sodium carbonate for 2 h. The mixture was cooled and saturated with NaCl; the aqueous layer was removed and replaced with 8 mL of fresh D_2O containing sodium carbonate and the cycle was repeated. After three cycles, ^1H NMR analysis indicated nearly complete exchange of the acetyl hydrogens, and the aqueous layer was saturated with NaCl and extracted with pentane. Bulb-to-bulb distillation (220 °C) of the concentrates gave approximately 600 mg of **16**-d_3. The ketone (5.2 mmol) was dissolved in 5 mL of anhydrous ether and added dropwise over 2 min to a stirred solution containing 100 mg (2.6 mmol) of $LiAlH_4$ in 4 mL of ether. After the mixture was stirred for 0.5 h, water was added carefully to destroy excess hydride, and the ether layer was collected, dried over Na_2SO_4, and concentrated; the residue was then distilled (bulb-to-bulb, ~210 °C) giving 480 mg (80%) of **37d**.

Carbinols 37a–c. Alcohols **37a–c** were obtained by reduction of the corresponding ketones **36a–c** with excess $LiAlH_4$ as described above in the preparation of **36d**. Products were purified by bulb-to-bulb distillation (140–170 °C (17 mm)) providing samples giving the spectral and analytical data which follows.

36a: IR (neat) 3400, 3320, 3060, 1055 cm^{-1}; NMR (CCl_4) δ −0.2–0.9 (m, 3 H, cyclopropyl), 0.97 (s, 3 H, CH_3C), 1.00 (m, 3 H, CH_3CH), 1.6–1.9 (m, 3 H, $CH_2C{\equiv}CH$), 2.27 (m, 2 H, CH_2CHOH), 2.83 (m, 1 H, CHOH).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.96; H, 10.70.

36b: IR (neat) 3390, 3080, 3060, 1640, 1450, 1062, 1020, 910 cm^{-1}; NMR (CCl_4) δ −0.2–0.8 (m, 3 H, cyclopropyl), 0.99 (s, 3 H, CH_3C), 1.01 (m, 3 H, CH_3CH), 1.63 (m, 2 H, CH_2CO), 2.10 (m,

(21) R. Rafcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).
(22) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).
(23) O. Diels and K. Pflaumer, *Chem. Ber.*, **48**, 223 (1915).
(24) H. Morrison, S. Danishefsky, and P. Yates, *J. Org. Chem.*, **26**, 2617 (1961).

2 H, allylic), 2.70 (m, 1 H, CHOH), 4.8–5.3 (m, 2 H, C=CH_2), 5.8–6.3 (m, 1 H, C=CH).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.59; H, 11.90.

36c: IR (neat) 3400 cm^{-1}; NMR (CCl_4) δ −0.2–0.8 (m, 3 H, cyclopropyl), 0.93 (t, 3 H, CH_3CH_2), 1.00 (s, 3 H, CH_3C), 1.03 (m, 3 H, CH_3CH), 1.2–1.6 (m, 6 H, methylene), 2.67 (m, 1 H, CHOH).

Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.96. Found: C, 76.77; H, 13.24.

Acetolyses of 36a–d. In each case approximately 100 mg of alcohol was dissolved in 4 mL of glacial acetic acid containing a drop of boron trifluoride etherate, and the solution was heated at 85 °C for 1.5 h. The mixtures were cooled, poured into water, and extracted with pentane. Extracts were washed with water, aqueous $NaHCO_3$, and finally water and then dried over Na_2SO_4. Solvent removal gave crude mixtures of **38** and **39** analyzed by ^1H NMR with the aid of $Eu(fod)_3$ (see Table I). Bulb-to-bulb distillation of the mixtures of isomeric acetates gave analytical samples affording the following data.

38a, 39a. Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.36; H, 9.49.

38b, 39b. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.28; H, 10.49.

38c, 39c. Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.61; H, 11.25.

8-Bromo-6-methyl-(*E*)-5-nonen-1-yne[9] (40a). Thirteen milliliters of a solution prepared by dissolving 7.0 g of $ZnBr_2$ in 5 mL of 48% HBr was cooled with a salt–ice bath, and, with vigorous stirring, 3.25 g (28 mmol) of **37a** was added over 5 min. The mixture was stirred at −15 °C for 15 min and then treated with 30 mL of pentane followed by 130 mL of cold water. The pentane extract was washed well with water, dilute $NaHCO_3$, water, and brine and dried over Na_2SO_4. Solvent removal gave 5.4 g (89%) of crude product. GLC analysis (column A, 125 °C) showed the mixture to contain approximately 92% of **40a** (T_r 6.2 min) and 8% of **41a** (T_r 5.9 min). The mixture was freed of solvent by bulb-to-bulb distillation (125 °C (1 mm)): NMR (CCl_4) δ 1.63 (m, 3 H, CH_3C=), 1.67 (d, 3 H, J = 6.8 Hz, CH_3CHBr), 2.1–2.3 (bm, 4 H, $-CH_2CH_2-$), 2.50 (dd, 2 H, $CBrCH_2$), 4.13 (m, 1 H, >CHBr), 5.25 (bm, 1 H, vinyl).

Anal. Calcd for $C_{10}H_{15}Br$: C, 55.83; H, 7.03. Found: C, 56.26; H, 7.20.

Rearrangement of 37a-d_1 under Johnson–Julia Conditions. 5-(*cis*-1,2-Dimethylcyclopropyl)-1-pentyn-5-ol-*5*-d_1 (**37a**-d_1) was prepared by the reduction of **36a** with $LiAlD_4$ as in the preparation of **37a**. Treatment of this alcohol with HBr–$ZnBr_2$ as described above in the preparation of **40a** gave the corresponding bromide mixture **40a**-d_1 and **41a**-d_1. The ^2H NMR spectrum of this sample contained peaks corresponding to vinyl D, >CDBr, and vinyl CH_2D in a ratio of 93:7:15.

5-Bromo-3-methyl-(*E*)-2-hexene (9). Treatment of **8** with HBr–$ZnBr_2$ as described above in the preparation of **40a** gave homoallylic bromide **9** as the sole product detectable by GLC analysis (column B, 80 °C). The bromide was freed of solvent by bulb-to-bulb distillation (115 °C (40 mm)): NMR (CCl_4) δ 1.50–1.65 (m, 6 H, vinyl CH_3), 1.63 (d, 3 H, J = 6.6 Hz, CH_3CH), 2.3–2.7 (m, 2 H, CH_2), 5.25 (bm, 1 H, vinyl).

Anal. Calcd for $C_7H_{13}Br$: C, 47.48; H, 7.40. Found: C, 47.51; H, 7.49.

Rearrangement of 8-d_1 under Johnson–Julia Conditions. 1-(*cis*-1,2-Dimethylcyclopropyl)ethanol-*1*-d_1 (**8**-d_1) was prepared by the reduction of **16** with $LiAlD_4$ as in the preparation of **37a**. Treatment of this alcohol with HBr–$ZnBr_2$ as in the preparation of **9** gave **9**-d_1. The ^2H NMR spectrum of this bromide contained three peaks corresponding to vinyl D, >CDBr, and vinyl CH_2D in the ratio of 55:45:4.

Acknowledgments. We express our sincere appreciation to Dr. G. B. Staal of Zoecon Corp. for helpful discussions and for verification of our bioassays.

Registry No. **1**, 66521-02-6; **4**, 70130-78-8; **5**, 70130-79-9; **6** isomer 1, 70130-80-2; **6** isomer 2, 70190-94-2; (*Z*)-**7**, 70130-81-3; (*E*)-**7**, 70130-82-4; **8** isomer 1, 70190-95-3; **8** isomer 2, 70190-96-4; **8**-d_1, 70130-83-5; **9**, 70130-84-6; **9**-d_1 isomer 1, 70130-85-7; **9**-d_1 isomer 2, 70130-86-8; **9**-d_1 isomer 3, 70130-87-9; (*E*)-**10**, 70130-88-0; (*Z*)-**10**, 70130-89-1; **16**, 70130-90-4; **16**-d_3, 70130-91-5; **17**, 70130-92-6; **19** isomer 1, 70130-93-7; **19** isomer 2, 70130-94-8; **20**, 70130-95-9; **21**, 70130-96-0; **21** *p*-nitrobenzoate, 70130-97-1; **22**, 70130-98-2; **23**, 70130-99-3; **24**, 70131-00-9; **25**, 70131-01-0; **26**, 70131-02-1; **26** diacetate, 70131-03-2; **27**, 70131-04-3; **27** diacetate, 70131-05-4; **28**, 70130-68-6; **28** diacetate, 70130-69-7; **29**, 70131-06-5; **36a**, 70131-07-6; **36b**, 70131-08-7; **36c**, 70131-09-8; **37a**, 42895-35-2; **37b**, 70131-10-1; **37c**, 70131-11-2; **37d**, 70131-12-3; **37a**-d_1, 70131-13-4; (*E*)-**38a**, 70131-14-5; (*Z*)-**38a**, 70131-15-6; (*E*)-**38b**, 70131-16-7; (*Z*)-**38b**, 70131-17-8; (*E*)-**38c**, 70131-18-9; (*Z*)-**38c**, 70131-19-0; (*E*)-**38d**, 70131-20-3; (*Z*)-**38d**, 70131-21-4; **39a**, 70131-22-5; **39b**, 70131-23-6; **39c**, 70131-24-7; **40a**, 70131-25-8; **40a**-d_1 isomer 1, 70131-26-9; **40a**-d_1 isomer 2, 70131-27-0; **40a**-d_1 isomer 3, 70131-28-1; **41a**, 70131-29-2; **41a**-d_1 isomer 1, 70131-30-5; **41a**-d_1 isomer 2, 70131-31-6; **41a**-d_1 isomer 3, 70131-32-7; diethyl carbonate, 105-58-8; biacetyl hydrazone, 33487-48-8; 3-diazo-2-butanone, 14088-58-5; propargyl bromide, 106-96-7; allyl bromide, 106-95-6; propyl iodide, 107-08-4.

Studies on Vindolinine. 6.† Partial Synthesis of Aspidospermane-Type Alkaloids[1,2]

Nicole Langlois* and Ratremaniaina Z. Andriamialisoa

Institut de Chimie des Substances Naturelles du C.N.R.S., 91190 Gif-sur-Yvette, France

Received November 8, 1978

19-Iodotabersonines (**2**) can be easily obtained from vindolinine (**1**). These compounds are shown to be useful intermediates especially via 19-oxotabersonine (**6**) in partial synthesis of several aspidospermane-type alkaloids. This procedure now allows the preparation of a number of alkaloids which can be isolated only in minute amounts from natural sources.

Vindolinine (**1**), whose structure has been revised mainly by ^{13}C NMR,[3] is one of the major monomeric alkaloids isolated from the Madagascan *Catharanthus* species and particularly from the most common and thoroughly studied of them *C. roseus*.[4] Fragmentation of **1** with iodine (THF–Na_2CO_3) has already been reported by us[1,5] and led mainly to a mixture of both epimeric 19-iodo-

† The authors wish to dedicate this work to memory of the late Professor J. Le Men.

(1) Part V: L. Diatta, R. Z. Andriamialisoa, N. Langlois, and P. Potier, *Tetrahedron*, **32**, 2839 (1976).

(2) Preliminary communications: (a) R. Z. Andriamialisoa and N. Langlois, "Les *Catharanthus*: importance des travaux francais", Tananarive, Sept. 1977; (b) N. Langlois, "Vindolinine, Etudes chimiques et hémi-synthèses", Reims, March 23, 1978.

0022-3263/79/1944-2468$01.00/0