from this and other results, i.e., adamantyl allenic retinal,[22] we had concluded that the β-ionone binding site[23] of bovine opsin is lenient in its steric requirement. The present result is thus the *first indication of chiral discrimination by the opsin.*[24]

Irradiation of the pigment (67 mM phosphate buffer, pH 7.0, 2% digitonin) with >510-nm light[25] resulted in disappearance of the 465-nm band in 4 h. Photolysis of the diazoacetoxy group, λ_{max} 245 nm, was carried out by irradiation of the pigment at 254 nm by using a 4-W[26] Hg lamp and narrow band pass interference filter at 25 °C. Since a 4-h irradiation resulted in only a ca. 10% decrease of the 465-nm peak, we believe that the specific interactions between chromophore and opsin in the binding sites (which are responsible for the characteristic absorption maximum) have not been considerably affected by irradiation at 254 nm. The amount of chromophore extracted by the CH_2Cl_2[27] method diminished successively with time so that after the 4-h irradiation it was only 15–30% of the nonirradiated control. This indicates that the diazoacetoxyl group has been photolyzed efficiently within the binding site. The extent of covalent binding to the protein will be determined quantitatively by ongoing studies with the pigment formed from 3-($O^{14}COCHN_2$)-labeled 9-*cis*-retinal.[28]

Registry No. 1, 81600-84-2; **2**, 14398-35-7; **3**, 81555-36-4; **4**, 81555-37-5; *cis*-**5**, 81555-38-6; *trans*-**5**, 81600-85-3; *cis*-6, 81600-86-4; *trans*-6, 81600-87-5; *syn*-**7**, 81583-45-1; *anti*-**7**, 81623-37-2.

(22) Blatchly, R. A.; Carriker, J. D.; Balogh-Nair, V.; Nakanishi, K. *J. Am. Chem. Soc.* **1980**, *102*, 2495.
(23) Matsumoto, H.; Yoshizawa, T. *Nature (London)* **1975**, *258*, 623.
(24) Studies are in progress to resolve the two enantiomeric retinals and to determine the absolute configuration of the enantiomer accepted by the protein.
(25) 1-kW Ushio projector lamp, 25-cm distance, 510-nm filter, room temperature.
(26) A weak intensity lamp was deliberately used to minimize the loss of the 465-nm absorption.
(27) The hexane-washed (11 times to remove excess unbound chromophore) pigment pellets each prepared from 2 OD opsin were extracted five times with CH_2Cl_2, and the CH_2Cl_2 extracts were combined and submitted to HPLC.
(28) The present studies were supported by NIH grant EY 01253.

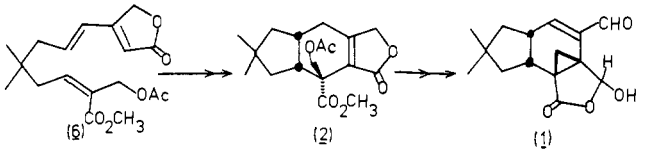
Stereocontrol in the Intramolecular Diels–Alder Reaction. 3. A Potentially General Method for the Synthesis of *cis*-Hydrindenes by Use of (*Z*)-Diene Units

Robert K. Boeckman, Jr.,* and Thomas R. Alessi

Department of Chemistry, University of Rochester Rochester, New York 14627

Received December 14, 1981

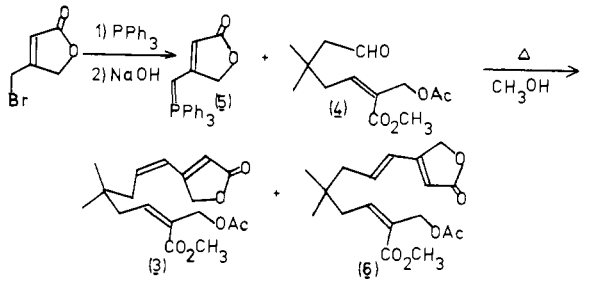
In a previous communication, we reported a convergent synthetic sequence to the unique sesquiterpene antibiotic marasmic acid (**1**), which utilized as the key element of the synthetic strategy an intramolecular Diels–Alder reaction to assemble the required *cis*-hydrindene skeleton (eq 1).[1]



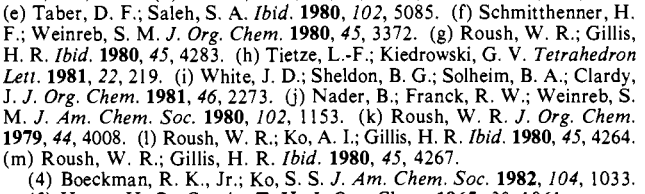
(1)

However, in spite of a large amount of work recorded in this area, especially by Roush[2,3] and ourselves,[1,4] a *general solution* to the problem of construction of *cis*-hydrindene nuclei with complete stereoselectivity via intramolecular cycloaddition has not become available.

Scheme I



We were attracted to the possibility that the use of (*Z*)-diene elements might provide such a solution, since it was apparent that other control elements such as dienophile geometry and stereoelectronic effects were insufficient energetically to impart the required levels of stereocontrol.[4] Bimolecular Diels–Alder reactions of (*Z*)-dienes are effectively unknown, and only two examples of the successful intramolecular cycloaddition of (*Z*)-dienes have thus far been reported.[5,6] These cases were examples of systems that were relatively unsubstituted or possessed highly activated dienophile groups. Consequently, the application to a highly substituted and less activated system such as that described herein would represent a stringent test of the methodology. It was further of interest to have a quantitative comparison of the relative reactivity of a pair of more highly functionalized but not unusually highly activated (*Z*)- and (*E*)-diene systems, since the apparently comparable rates of cyclization for *E* and *Z* isomers observed by House appeared to violate intuition.[5] Most importantly, the studies reported herein examine the validity of concern over a potentially serious limitation on the method indirectly suggested by the studies of Borch.[7] Competition between thermally allowed 1,5 sigmatropic hydrogen shifts and cycloaddition, formally possible in nearly all (*Z*)-diene systems, could result in loss of the geometric or structural integrity of the diene as shown schematically in eq 2.



(2)

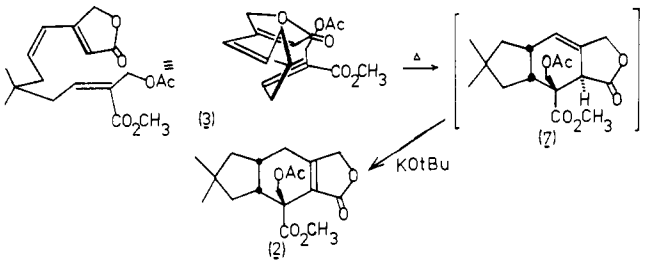
We report the successful use of a (*Z*)-diene unit as the control element in the highly substituted triene **3** to the *completely stereoselective* construction of the highly functionalized *cis*-lactone **2**, which has previously been transformed to marasmic acid (**1**). The (*Z*,*Z*,*Z*)-triene **3** was prepared from known precursors as shown in Scheme I.[8] Treatment of the aldehyde **4** (1 equiv) with

(1) Boeckman, R. K., Jr.; Ko, S. S. *J. Am. Chem. Soc.* **1980**, *102*, 7146.
(2) Reviews: (a) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. (b) Oppolzer, W. *Synthesis* **1978**, 793. (c) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. (d) Funk, R. L.; Vollhardt, K. P. C. *Chem. Soc. Rev.* **1980**, *9*, 41. (e) Carlson, R. G. *Ann. Rep. Med. Chem.* **1974**, *9*, 270.
(3) A few recent examples: (a) Snowden, R. L. *Tetrahedron Lett.* **1981**, *22*, 97, 101. (b) Wilson, S. R.; Misra, R. N. *J. Org. Chem.* **1980**, *45*, 5079. (c) Ichihara, A.; Kimura, R.; Yamada, S.; Sakamura, S. *J. Am. Chem. Soc.* **1980**, *102*, 6353. (d) Martin, S. F.; Tu, C.; Chou, T. *Ibid.* **1980**, *102*, 5274. (e) Taber, D. F.; Saleh, S. A. *Ibid.* **1980**, *102*, 5085. (f) Schmitthenner, H. F.; Weinreb, S. M. *J. Org. Chem.* **1980**, *45*, 3372. (g) Roush, W. R.; Gillis, H. R. *Ibid.* **1980**, *45*, 4283. (h) Tietze, L.-F.; Kiedrowski, G. V. *Tetrahedron Lett.* **1981**, *22*, 219. (i) White, J. D.; Sheldon, B. G.; Solheim, B. A.; Clardy, J. *J. Org. Chem.* **1981**, *46*, 2273. (j) Nader, B.; Franck, R. W.; Weinreb, S. M. *J. Am. Chem. Soc.* **1980**, *102*, 1153. (k) Roush, W. R. *J. Org. Chem.* **1979**, *44*, 4008. (l) Roush, W. R.; Ko, A. I.; Gillis, H. R. *Ibid.* **1980**, *45*, 4264. (m) Roush, W. R.; Gillis, H. R. *Ibid.* **1980**, *45*, 4267.
(4) Boeckman, R. K., Jr.; Ko, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 1033.
(5) House, H. O.; Cronin, T. H. *J. Org. Chem.* **1965**, *30*, 1061.
(6) Pyne, S. G.; Hensel, M. J.; Byrn, S. R.; McKenzie, A. T.; Fuchs, P. L. *J. Am. Chem. Soc.* **1980**, *102*, 5960.
(7) (a) Borch, R. F.; Evans, A. J.; Wade, J. J. *J. Am. Chem. Soc.* **1975**, *97*, 6282. (b) Borch, R. F.; Evans, A. J.; Wade, J. J. *Ibid.* **1977**, *99*, 1612.
(8) **3**: IR ($CHCl_3$) 1780, 1755, 1725, 1640 cm^{-1}; NMR ($CDCl_3$/400 MHz) δ 6.33 (t, J = 7.8 Hz, 1), 6.21 (d, J = 11.7 Hz, 1), 6.11 (dt, J = 11.7 Hz, J_2 = 7.3 Hz, 1), 5.98 (s, 1), 4.95 (s, 2), 4.75 (s, 2), 3.77 (s, 3), 2.58 (d, J = 7.8 Hz, 2), 2.20 (d, J = 7.3 Hz, 2), 2.07 (s, 3), 1.00 (s, 6). **5**: IR ($CDCl_3$) 1685 cm^{-1}; NMR ($CDCl_3$/90 MHz) δ 7.46 (m, 16 H), 4.73 (s, 2), 4.15 (s, 1).

0002-7863/82/1504-3216$01.25/0

the stabilized ylide **5** (2 equiv) (obtained from the corresponding (bromomethyl)butenolide[9] as shown) in methanol/CH_2Cl_2 (1:4) at reflux (3.5 h) afforded **3** and the related trans-isomer **6** (5:1) in 65% yield.[10]

Thermolysis of **3** was conducted at ~230 °C (sealed tube in toluene) for 32 h. Treatment of the crude product with KO-*t*-Bu/ether and workup afforded cleanly a single cycloadduct, the cis-conjugated lactone **2**, in 80% yield. This substance was shown to be identical with an authentic sample of lactone **2** by 400-MHz NMR and all other criteria.[1] No evidence of the formation of any other isomeric cycloadducts was observed.[11] In this instance, at elevated temperatures, partial conjugation of the primary cycloadduct **7** occurred as was observed in the cyclization of the related (*Z*,*E*,*Z*)-triene (eq 3).



(3)

It was also confirmed that the cyclization of **3** proceeds significantly more slowly than for the related *Z*,*E*,*Z* isomer, as would be anticipated on steric grounds. We have measured the relative rates of cyclization of the (*Z*,*Z*,*Z*)- and (*Z*,*E*,*Z*)-trienes at 205 °C, and the latter is more reactive by a factor of ~42 ($t_{1/2}$ 76.6 h vs. $t_{1/2}$ 1.81 h) as expected. On this basis, we estimate the difference in activation energy ($\Delta\Delta G^{\ddagger}$) to be about 3.5 kcal/mol at 205 °C.[12,13] This difference, while significant, appears smaller than one might have anticipated by analogy to conceivable bimolecular reactions.

These results, for the highly functionalized and somewhat deactivated (*Z*)-diene system **3** *substantially extend the scope of these cyclizations and suggests that the approach will likely prove a general one.* Furthermore, these results serve to point out in striking fashion several significant generalizations regarding the use of (*Z*)-dienes: (1) transition-state selection is primarily governed by diene geometry; (2) dienophile orientation is independent of dienophile geometry; (3) the dienophile orientation has no great effect on the overall activation energy; (4) 1,5 sigmatropic hydrogen shifts and other isomerizations apparently do not present a limitation even in highly substituted systems.

Thus, the completely stereoselective cycloaddition (**3** → **2**) provides the basis for further experiments to exploit this general approach to cis-fused polycyclic ring systems for the synthesis of natural products.

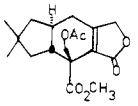
Acknowledgment. This investigation was supported by a research grant, GM-29290, from the Institute for General Medical Sciences of the National Institutes of Health, to whom we are extremely grateful. We also thank the NSF for a grant in support of the acquisition of the Bruker WH-400 400 MHz NMR spectrometer.

Registry No. 2, 81600-71-7; **3**, 81554-04-3; **4**, 75887-41-1; **5**, 81554-05-4; 6, 75887-44-4; (bromomethyl)butenolide, 61934-55-2.

(9) Martin, R.; Chapleo, C. B.; Svanholt, K. L.; Dreiding, A. S. *Helv. Chim. Acta* **1976**, *59*, 2724.

(10) House, H. O.; Jones, V. K.; Frank, G. *J. Org. Chem.* **1964**, *29*, 3327.

(11) Separation of the isomeric dienes is tedious, and so for preparative purposes cyclization can be conducted on the 5:1 mixture of (*Z*,*Z*,*Z*)- and (*Z*,*E*,*Z*)-trienes, which affords, after treatment with *t*-BuOK, a readily separable mixture of **2** and **6** (~11:1). It should be pointed out that, in this case, the practical limit on stereoselectivity resides in geometric selectivity observed in the *production* of the (*Z*)-diene. Methodology for the construction of (*Z*)-dienes with high geometric specificity is under investigation in our laboratories.



i

(12) Measured by NMR (400 MHz) by repetitive integration of diagnostic peaks in the olefin region of compounds **2** and **3**. The values for half-lives were derived from least-squares treatment of the data points for 3 or more half-lives. The reactions showed good first-order kinetics (within experimental error), and values for the half-lives are the average results of duplicate determinations.

(13) The observed differences for our system may be rather structure dependent, due in part to the relative rigidity of the diene system, although the fact that the C-2 diene substituent is tied back in a ring and the diene is carbonyl conjugated would appear to result in decreased rather than increased reactivity. Activation parameters are certainly structure dependent as shown by the cyclization of the system studied by Fuchs at 110 °C.[6]

Biosynthesis of Sulfur Compounds. Elucidation of the Stereochemistry of the Conversion of [3-(Methylthio)propyl]glucosinolate into Allylglucosinolate (Sinigrin)

Ronald J. Parry* and M. V. Naidu

Department of Chemistry, Rice University
Houston, Texas 77251

Received March 1, 1982

The mustard oil glucoside allylglucosinolate (sinigrin) (**1**) is a common constituent of plants of the mustard family (*Cruciferae*).[1] The biosynthesis of **1** in horseradish (*Armoracia lapathifolia* Gilib.) has been shown[2,3] to proceed from homomethionine (**2**) via [3-(methylthio)propyl]glucosinolate (**3**) (Scheme I). [3-(Methylsulfinyl)propyl]glucosinolate (**4**) was also found to be a highly efficient precursor of allylglucosinolate. The transformation of **3** into **1** is an unusual biochemical reaction for which at least three possible mechanisms can be envisioned (Scheme II). One mechanism would proceed by the β-elimination of methanethiol (path a). A more likely mechanism (path b) could involve the conversion of **3** into a sulfonium salt followed by β-elimination of an alkyl methyl sulfide. Finally, a third mechanism (path c) could proceed via the pericyclic elimination of methanesulfenic acid from the sulfoxide **4**. This last pathway would be of particular interest since there are no established examples of enzyme-catalyzed pericyclic reactions, with the possible exception of chorismate mutase.[4] In principle, a distinction between the pericyclic reaction pathway (c) and the two alternatives might be achieved by elucidation of the stereochemistry of the elimination process. The pericyclic route must proceed by a syn-elimination mechanism, while paths a and b could follow either a syn or anti geometry, with anti geometry being more likely.[5] We now report the results of experiments that rule out a pericyclic elimination process in the biosynthesis of allylglucosinolate.

The elucidation of the stereochemistry of the elimination reaction was accomplished in two stages by precursor incorporation experiments with chirally labeled forms of homomethionine. The first stage utilized DL-[4(*RS*)-, 4(*R*)-, and 4(*S*)-^{3}H]homomethionine. The synthesis of these labeled amino acids was accomplished as outlined in Scheme III. Benzyloxybenzaldehyde, prepared in 56% yield by DCC/Me_2SO oxidation[6,7] of benzyl-

(1) (a) Kjaer, A. *Fortschr. Chem. Org. Naturst.* **1960**, *18*, 122. (b) Ettlinger, M. G.; Kjaer, A., in *Recent Adv. Phytochem.* **1968**, *1*, 58.

(2) Matsuo, M.; Yamazaki, M. *Chem. Pharm. Bull.* **1968**, *16*, 1034.

(3) Chisholm, M. D.; Matsuo, M. *Phytochem.* **1972**, *11*, 203.

(4) Andrews, P. R.; Cain, E. N.; Rizzardo, E.; Smith, G. D. *Biochemistry* **1977**, *16*, 4848.

(5) Hanson, K. R.; Rose, I. A. *Acc. Chem. Res.* **1975**, *8*, 1.

(6) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1963**, *85*, 3027.

(7) Attempts to achieve this oxidation with the Collins reagent or PCC were unsuccessful.

0002-7863/82/1504-3217$01.25/0