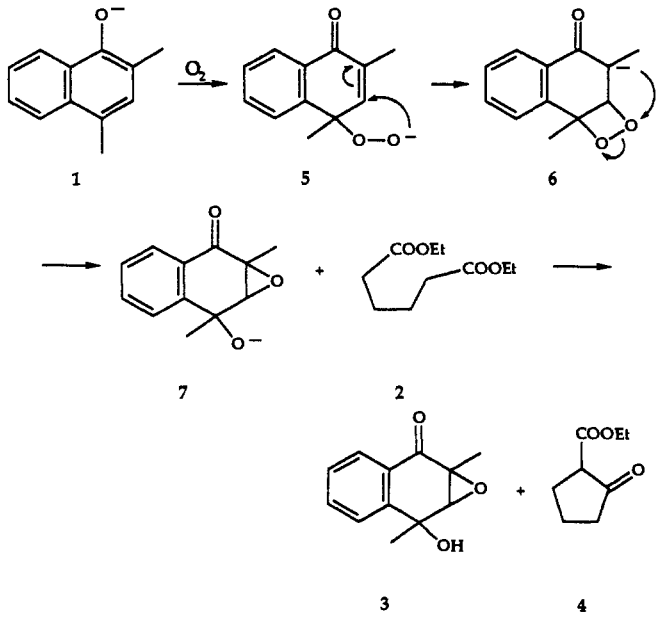
Scheme III

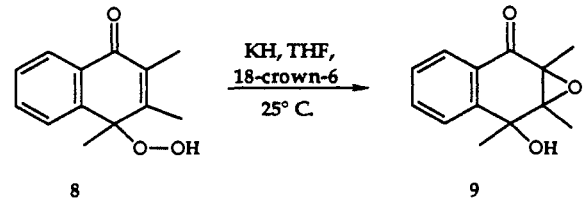


from the mechanistic picture is a working chemical model to show if, what, and how vitamin K oxide formation contributes to the condensation reaction.

We have discovered a new nonenzymic model which mimics the essential features of the vitamin K dependent condensation. Thus, when a THF solution of diethyl adipate (**2**) is treated at room temperature with potassium 2,4-dimethyl-1-naphthoxide (**1**) and 1.7 equiv of oxygen, bubbled in over a period of 3 h with a gas-tight syringe,[18] in the presence of 18-crown-6 (Scheme II), condensation (internal carboxylation) occurs to yield the 1-oxocyclopentane-2-carboxylate **4** (30–35%) and the keto epoxide **3** (50–60%).[19,20] When oxygen is excluded from the reaction, *no cyclization* of diethyl adipate (**2**) to ethyl 1-oxocyclopentane-2-carboxylate (**4**) occurs; less than 1% of **4** can readily be detected in the NMR spectrum of the total crude reaction product, and of course, none of the epoxide **3** is formed. Indeed, the oxygen-free control must be scrupulously carried out; otherwise, traces of cyclized product **4** are produced by small amounts of adventitious oxygen.

We suggest that the following sequence of events takes place (Scheme III). The naphthoxide **1** reacts *spontaneously* with oxygen, yielding the hydroperoxy anion **5**, which undergoes internal dioxetane formation to **6**. That step is followed by transformation of **6** to the epoxy alkoxide **7**,[21] which is a strong base and effects the condensation reaction of **2** to **4**. The naphthoxide **1** is not sufficiently basic to effect the condensation of **2** to **4**. Likewise, neither potassium *tert*-butylperoxide[16] nor potassium superoxide is sufficiently basic to effect the condensation of **2** to **4** under the reaction conditions used for the model in Scheme II.

To explore further the rearrangement of the hydroperoxy anion **5** to the oxide **7**, the stable hydroperoxide **8** was prepared by treatment of 2,3,4-trimethyl-1-naphthol with oxygen in chloroform.[22] When **8** is treated at room temperature with potassium hydride and 18-crown-6 in THF, rearrangement to the keto epoxide **9** occurs.



We propose that epoxidation is an *integral part of the vitamin K dependent carboxylation reaction*, driving the reaction by transforming the biologically accessible but weakly basic naphthoxide anion to the biologically remote but strongly basic alkoxide anion. The energy gained from converting the weak peroxide bond to the relatively strong carbon–oxygen bond of the epoxide is coupled to and bridges the energy gap between the weak naphthoxide and the strong alkoxide bases.

This is the first nonenzymic model mimicking the *carbon–carbon-bond-forming condensation reaction* dependent on vitamin K and leading to a keto epoxide. The model introduces *a novel basicity enhancement reaction* which may be the key to understanding how vitamin K functions and may have extensions to other chemical and biochemical transformations. Finally, this model suggests that *molecular oxygen is the initiating factor* in the vitamin K dependent carboxylation sequence.

Acknowledgment. This research was supported by the National Science Foundation. We thank Dr. Roger Hershline and Patricia Cottam for early experiments in this area, Professor Chien Ho for the use of his laboratory facilities, and Dr. S.-C. Choi for his assistance at a later stage of the research.

(16) Lawson and Suttie proposed that a hydroperoxide anion might be sufficiently basic to produce a carbanion intermediate: Lawson, A. E.; Suttie, J. W. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *75*, 5413. This conclusion has been contested by Olson et al.; Olson, R. E.; Hall, A. L.; Lee, F. C.; Kappel, W. K.; Meyer, R. G.; Bettger, W. J. In *Posttranslational Covalent Modification of Proteins*; Connor Johnson, B., Ed.; Academic Press: New York, 1983; pp 295–319. Hall, A. L.; Kloepper, R.; Zee-Chang, R. K.-Y.; Lee, F. C.; Olson, R. E. *Arch. Biochem. Biophys.* **1982**, *214*, 45.

(17) For an acetyl transfer reaction originating from a vitamin K hydroperoxide analogue, see: Wilson, R. M.; Tharp, G. *J. Am. Chem. Soc.* **1985**, *107*, 4100.

(18) It is important to limit the amount of oxygen and to add it slowly. Use of excess oxygen led to epoxy ketone **3** but yielded little or no cyclic product **4**.

(19) Yields are those of pure isolated products. All new substances exhibited satisfactory spectral properties.

(20) Diethyl pimelate was also successfully cyclized to 1-oxocyclohexane-2-carboxylate under the conditions of the transformation in Scheme II.

(21) Nishinaga, A.; Itahara, T.; Shimizu, T.; Matsuura, T. *J. Am. Chem. Soc.* **1978**, *100*, 1820. Griesshammer, R.; Schneider, H. P.; Winter, W.; Rieker, A. *Tetrahedron Lett.* **1979**, 3941.

(22) Greenland, H.; Pinhey, J. T.; Sternhell, S. *Aust. J. Chem.* **1987**, *40*, 325.

The Allylic Epoxide Cyclization. A Method for the Control of Regiochemistry and Stereochemistry in Cyclohexane Systems

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We have developed a new method of vicinal stereocontrol, which we illustrate by the regio- and stereoselective transformations shown in eqs 1 and 2.

The reaction translates the stereochemistry of a simple trans epoxide into the stereocontrolled formation of three contiguous asymmetric centers, one of which is quaternary; it leads to products (cf. **2**, **4**, **5**) with well-differentiated functions which can easily be elaborated in various directions; and finally, it readily leads to homochiral products because of the availability of epoxides such as **7** (vide infra) in known absolute configuration.

The regio- and stereochemical results illustrated, for example, by **1** → **2** and **3** → **4** deserve comment.

The normal propensity observed in the intramolecular opening of an epoxide by a carbanion is for displacement to occur at the proximal end, with the resulting formation of the smaller carbocycle.[1] The desired formation of a cyclohexane rather than a cyclopentane ring could be achieved with trans-disubstituted

(1) (a) Stork, G.; Cama, L. D.; Coulson, D. R. *J. Am. Chem. Soc.* **1974**, *96*, 5268. Stork, G.; Cohen, J. F. *J. Am. Chem. Soc.* **1974**, *96*, 5270. (b) Lallemand, J. Y.; Onanga, M. *Tetrahedron Lett.* **1975**, 585.

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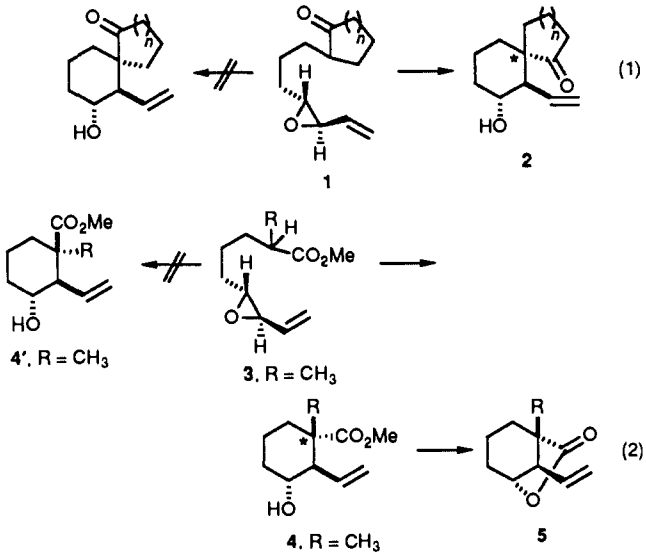
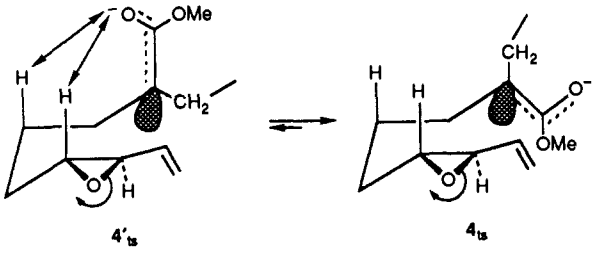


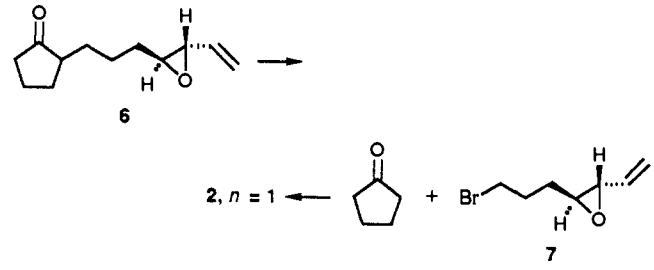
epoxides,[2] however, simply by making the distal end of the epoxide part of an allylic system,[3] as shown in eqs 1 and 2.

The trans stereochemistry of the vicinal vinyl and hydroxyl groups in the products is, of course, the corollary of the anticipated concerted opening of trans-disubstituted epoxides such as **1** and **3**. The striking stereoselectivity at the newly formed quaternary center (starred in **2** and **4**) is of less obvious origin. It is unrelated to product stability, since the energy difference between the two epimers, especially **4** vs **4′**, would, if anything, favor **4′**.

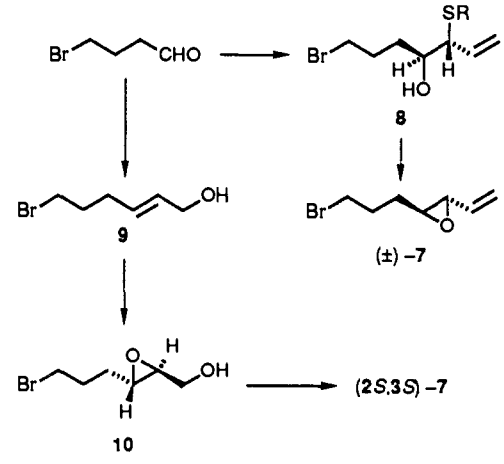
A plausible interpretation of the observed stereoselectivity follows from the requirement that the carbanion orbital must remain perpendicular to the carbonyl plane in the transition state for the epoxide opening. In a chair-like transition state, the axial orientation of the enolate shown in $4'_{ts}$ would result in severe 1,3-diaxial interactions, resembling those of a *tert*-butyl group. A transition state like $\mathbf{4}_{ts}$, with the enolate system in an equatorial arrangement, is then preferred, with the result that **2** and **4** are formed stereoselectively.[4]



We originally constructed the epoxy ketone **6** by side-chain elaboration, starting with the readily available methyl 3-(2-oxocyclopentyl)propionate,[5] and were pleased to find that pure **6** cyclizes (potassium *tert*-butoxide/THF, 0 °C, then 1 h at room temperature) to give, stereospecifically, the spiro ketol **2**, $n = 1$, *in 95% yield*. The syn relationship of the carbonyl and the secondary hydroxyl was established by the transformation of **2**, $n = 1$, after hydrogenation, to the γ-lactone **5**, R = 2-carbomethoxyethyl (ethyl rather than vinyl on the methylene bridge).[6]



We later developed a much simpler and more efficient construction of starting materials of this type. This involves the direct introduction at the α-position of ketones or esters of the required vinyl epoxide side chain, such as *trans*-3-(3-bromopropyl)-2-ethenyloxirane (**7**). The latter could be assembled easily, either in (±) or homochiral form. The (±)-**7** was prepared in 50% overall yield from 4-bromobutyraldehyde by Yamamoto's method,[7] via the carbinol **8**. Homochiral **7**, either 2*S*,3*S* or 2*R*,3*R*, was readily made by Sharpless expoxidation[8] of allylic alcohol **9**. With L-(+)-diethyl tartrate as catalyst, essentially pure (2*S*,3*S*)-3-(3-bromopropyl)-2-oxiranemethanol (**10**), $[\alpha]_D$ −23.3° (ethanol, $c = 7$), was obtained and could then be converted, in 65% overall yield, to (2*S*,3*S*)-**7** by Swern oxidation, followed by Wittig reaction.



Reaction of cyclopentanone (2 equiv) with (±)-**7** (1 equiv) (4 equiv of KH in THF at 0 °C → room temperature, 75 min) directly gave the spiro ketol **2**, $n = 1$, in 50% yield. Cyclohexanone similarly gave the homologous spiro ketol **2**, $n = 2$, in the same yield.

The stereoselective allylic epoxide cyclization is especially noteworthy with esters (cf. **3** → **4**) because it can be allowed to proceed to the formation of the corresponding lactones **5**, thus

(2) For a related case of regiochemical control in an *intermolecular* displacement at a benzylic epoxide, see: van Tamelen, E. E.; Van Zyl, G.; Zuidema, G. D. *J. Am. Chem. Soc.* **1950**, *72*, 488. For a recent application of the same principle to the formation of tetrahydropyran systems, see: Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 6676.

(3) Cis-disubstituted allylic epoxides give *five-membered* rings in this cyclization. An effect of epoxide stereochemistry on the partition between the four- and five-membered rings resulting from the cyclization of saturated δ,ε-epoxy nitriles has been noted previously: cf. ref. 1b.

(4) Figure $4'_{ts}$ represents the enolate of an ester like **3**. For a ketone (cf. **1**), OMe = CH_2R. The possible relevance of this conformational argument in these cyclizations was first pointed out to us by Dr. Scott Biller, in this laboratory. It is consistent with this rationale that we found that the cyano analogue of ester **3**, in which the linear nature of the cyano group greatly reduces the interferences shown in $4'_{ts}$, gives a mixture of the cyclization products corresponding to **4** and **4′**, *in which the latter actually predominates*.

(5) The (oxocyclopentyl)propionate was elaborated into the epoxy ketone **6** by the following sequence: (a) $NaBH_4$; (b) TBDMSCl; (c) LAH; (d) CH_3SO_2Cl; (e) NaI; (f) $LiC{\equiv}CCH_2OLi$; (g) LAH/THF; (h) $VO(acac)_2$, *t*-BuOOH; (i) Swern oxidation; (j) $CH_3P^+Ph_3I^-$, $KN(SiMe_3)_2$; (k) $Bu_4N^+F^-$/THF; (l) PCC, NaOAc. The resulting **5** was purified by chromatography on deactivated basic alumina (10 g of water/100 g of alumina).

(6) Reduction (Pd/C, H_2) of vinyl to ethyl was followed by condensation with ethyl formate (NaOMe, THF, 80 min). The hydroxymethylene derivative was then oxidized (ozone, 1:5 methanol–methylene chloride, −70 °C, 30 min, then, after addition of acetic acid, with hydrogen peroxide at room temperature, 2 h) to the lactonic acid. The methyl ester of dihydro-**5**, R = 2-carbomethoxyethyl (ethyl instead of vinyl) had the following characteristics: IR ($CHCl_3$) ν_{CO} 1766, 1731 cm^{-1}; ^1H NMR ($CHCl_3$) δ 4.65 (t, $J = 5$ Hz), 3.62 (s), 2.31 (t, $J = 8$ Hz), 2.21–1.31 (m), 0.913 (t, $J = 7.4$ Hz); MS (CI, NH_3) 258 (M + 18), 241 (M + 1).

(7) Furuta, K.; Ikeda, Y.; Meguriya, N.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2781.

(8) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(9) The application of this process has led to the total synthesis of natural histrionicotoxin: Stork, G.; Zhao, K. Manuscript in preparation.

simplifying separation from any small amounts of epimeric by-products. As an illustration, treatment of the (±) ester **3** with 1.5 equiv of lithium hexamethyldisilazide in THF (−10 °C, 10 min, and 2.5 h at room temperature) gave the pure lactone **5**, R = CH_3, in 60% yield.[9]

We have examined a number of related cyclizations and can summarize our observations as follows: stereoselective formation of six-membered rings seems general with trans-disubstituted epoxides,[2] as in **1** and **3**; it is compatible with R groups of varying lengths, as well as with *E*- or *Z*-disubstituted homologues of the terminal vinyl groups of **1** and **3**; and finally, cyclization proceeded in the same manner when a disubstituted ethynyl group was present in place of the vinyl group.

Acknowledgment. We thank Drs. H. J. Schostarez and F. Pulido for contributions related to this work and the National Institutes of Health and the National Science Foundation for their support.

Supplementary Material Available: Schemes detailing the general cyclization procedures and the preparation of (±)-**7** as well as of (2*S*,3*S*)-**7**, lactone **5**, and spiro ketols **2**, $n = 1$ and $n = 2$, together with the related spectral data (25 pages). Ordering information is given on any current masthead page.

Computer Software Reviews

DISFREE. Biosoft: P.O. Box 580, Milltown, NJ 08850. List price $395.00.

DISFREE is a software package for nonparametric, or distribution-free, statistics. The program requires an IBM-XT, AT, or any compatible machine. This review was conducted primarily on an XT equipped with CGA, 8087 math coprocessor, and dot matrix printer. A Zenith PC with a monochrome monitor was also successfully used.

The package comes on 3.5 in. and 5.25 in. floppy disks that are not copy-protected; purchasers are permitted to make a single backup copy, but further distribution is not allowed. Also provided is an 88-page manual, but no mention is made of any further user support. In the Introduction to the manual the reader is informed that the software is based entirely on the book *Distribution-free Statistics—An Application-oriented Approach*, by Joachim Krauth (Elsevier: Amsterdam, 1988). There is a not-so-subtle admonition to have this book on hand, owing to the fact that many of the tests known from the literature have been modified and others are described here for the first time. An abbreviated listing of the more than 30 tests is given below; each has separate versions for large and small sample sizes, and the 25 most complex tests also allow for computation through simulations:

Two-sample tests of heterogeneity: Fisher-Pitman randomization test, Wilcoxon's rank-sum test, Gehan's test, McNemar's test, Lehmacher's test, Bowker's test.

Two-sample tests of dependence: Spearman's rank correlation test, Contingency-table test, Rank correlation test for censored data, Fisher's contingency-table test for variables with more than two categories.

Tests of heterogeneity for three or more samples: Kruskal-Wallis test, Schemper's test, Patel-Hoel test, Pitman-Welch test, Friedman's test, Wall's test.

For each of these, the manual lists the purpose of the test, the required data input, restrictions (sample size, etc.), output, interpretation of results, and finally some remarks. The fact that this is a very abbreviated treatment argues all the more for having the aforementioned book on hand before using this software. The following restrictions on input data are listed: A maximum of 10 groups of subjects with a maximum sample size in each group of 500. With contingency tables the maximum number of categories is 10 and the maximum sample size is 10000 for the small-sample procedure and 5000 for the simulation procedure. The largest possible cell frequency is 9999, and in the case of multivariate contingency tables you may have a maximum of 6 categories for 5 groups, 4 categories for 6 groups, 3 categories for 7 and 8 groups, and 2 categories for 9 and 10 groups.

Installation on the hard drive was easy, and the program appeared to execute flawlessly. The menu-driven format allows for input (and editing) of data as well as selection of the desired test. There is no provision for importing data. However, the files constructed by the DISFREE editor appear to be uncomplicated, and it should be possible to modify existing data files to be compatible with DISFREE. Only a few of the tests were tried in the course of this review. Those seemed to work properly, but in some cases run times were very long. Upon exiting the program it was found that some other software, e.g. WordPerfect 5.0, would not run on the XT without a warm restart. (Biosoft states that the problem has been overcome.)

This package will be of more value to researchers in the social sciences than to chemists. Most chemical data can be measured on some quantitative scale and is thus amenable to analysis by parametric methods. The social scientists, on the other hand, often have data that are susceptible to ordering but cannot be so readily quantitated. For those familiar with SPSS/PC+, it should be noted that the 16 tests found in procedure NPAR TESTS partly duplicate those in DISFREE.

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