THE CHEMISTRY OF CYCLIC VINYL ETHERS 4: CYCLIZATION OF UNSATURATED CYCLIC VINYL ETHER EPOXIDES[1]

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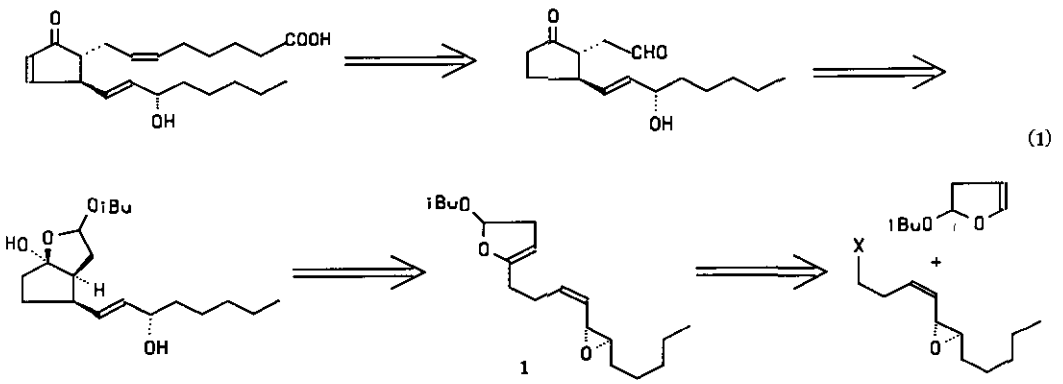
Abstract — The synthesis of [3Z,5S,6S] 2-[5,6-epoxy-undec-3-en-1-yl]-5,6-dihydro-4H-pyran (2) and [3Z,5S,6R] 2-[5,6-epoxy-undec-3-en-1-yl]-3,4-dihydrofuran (3) is outlined. Cyclization reactions of 2 and 3 catalyzed by various Lewis acids which proceed to afford spirocyclic ketals rather than the desired carbocycles are described.

We have previously reported the metalation of a variety of cyclic vinyl ethers and the utility of such intermediate anions as equivalents of the corresponding acyl anions.[1] Furthermore, we had reported sometime ago the results of initial studies of the intramolecular cyclization of cyclic vinyl ether-epoxides which are readily available by alkylation of vinyl ether anions with epoxy halides.[2,3] Indeed, the versatility of intramolecular cation-olefin cyclizations for the con-struction of carbocyclic rings had been elegantly demonstrated by Johnson and others.[4] As an extension of our previous studies, we have explored the feasibility of the extremely short enantioselective approach to the primary prostaglandins outlined in Eq 1.

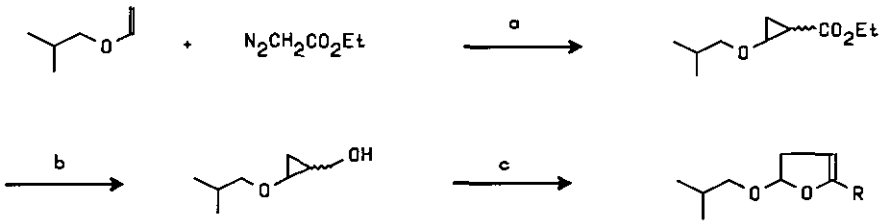


Our ideal cyclization substrate was envisioned to be the Z α'-alkoxydihydrofuran **1**. The choice of the Z,E mono-epoxide for the side chain was based upon the elegant studies of the Roussel-Uclaf group which demonstrated that this combination produces the required C_{12}(R), C_{15}(S) configuration found in the natural prostaglandins.[5] The crucial transformation then involves the participation of an endocyclic vinyl ether double bond as the nucleophile in a hopefully highly SYN stereoselective intramolecular S_N2' addition to a suitably activated vinyl epoxide.[6] We

envisioned that the endocyclic vinyl ether double bond would function as a masked enolate equivalent and the ensuing cyclization would effectively represent the equivalent of a regiospecific enolate alkylation. The resulting acetal upon hydrolysis was expected to provide for introduction of the required α side chain by means of well-precedented Wittig chemistry.[7] We describe below the preparation and attempted cyclization of two such substrates, dihydropyran **2** and dihydrofuran **3**.

Our initial efforts were directed at obtaining the substrate **1**, since we considered that the α'-alkoxy substituent would enhance the nucleophilicity of the endocyclic vinyl ether and provide additional stabilization of the developing charge in the oxonium ion intermediate. The required isobutoxy dihydrofuran **4** was prepared *via* the sequence outlined in Scheme 1. The key step involved oxidation of a cyclopropyl carbinol with Ag_2CO_3 on celite

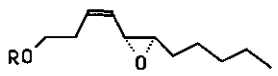
SCHEME 1[a]



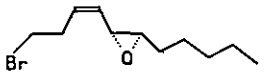
4 R = H
7 R = Li

[a]**Reagents:**
a) Cu (Bronze)/ Δ/ 16h; b) LAH/ Et_2O/ Δ/ 3h; c) Ag_2CO_3-celite/ PhH/ Δ/ 3h.

(Fetizon's reagent)[8] *which is accompanied by in situ rearrangement* of the resulting cyclopropylaldehyde to dihydrofuran **4** (40% overall from isobutyl vinyl ether) as described by Wenkert.[9] However, attempted alkylation of the epoxymesylate **5**, obtained by mesylation of the known alcohol **6**,[5] with α-lithiodihydrofuran **7** (obtained by metalation of **4** with t-BuLi (3 equiv) at 0°C in THF) failed to provide any of the expected dihydrofuran **1** under a variety of conditions. Quenching studies with D_2O suggested that proton transfer between the highly basic vinyl



5 R = SO_2CH_3
6 R = H
8 R = SO_2PhCH_3



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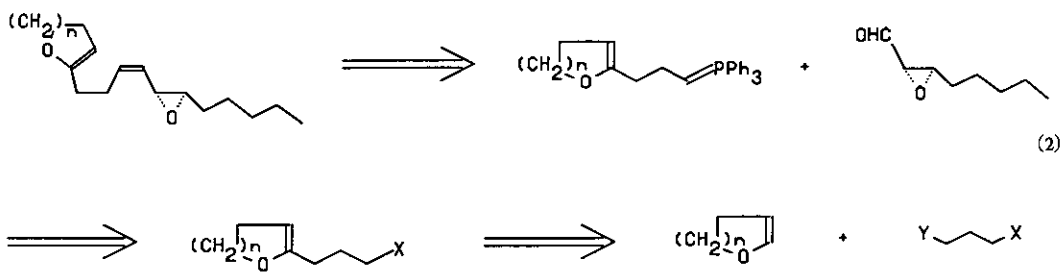
ether anion and the α-sulfonyl protons of the mesylate was occurring. Remarkably, when the related epoxy-tosylate **8** was employed again only proton transfer was observed.[10] Furthermore, we were unable to obtain the related epoxyiodide **9** by displacement due to the acid sensitivity of the allylic epoxide unit. Thus, we abandoned preparation of the more complex and highly sensitive substrate **1** in favor of the less functionalized substrates **2** and **3**.

We next investigated an alternative route involving the coupling of a suitable vinyl ether ylide with an appropriate α-epoxyaldehyde as outlined in Eq 2. This sequence was particularly attractive since Wittig coupling was expected to selectively afford the required Z epoxyolefin, and the route seemed amenable to the preparation of the required substrates in optically active form.[11] Since the preparation of the multifunctional phosphonium salts required for this strategy was not well precedented, we focussed initially on the preparation of the simpler derivatives dihydropyran **2** and dihydrofuran **3**.

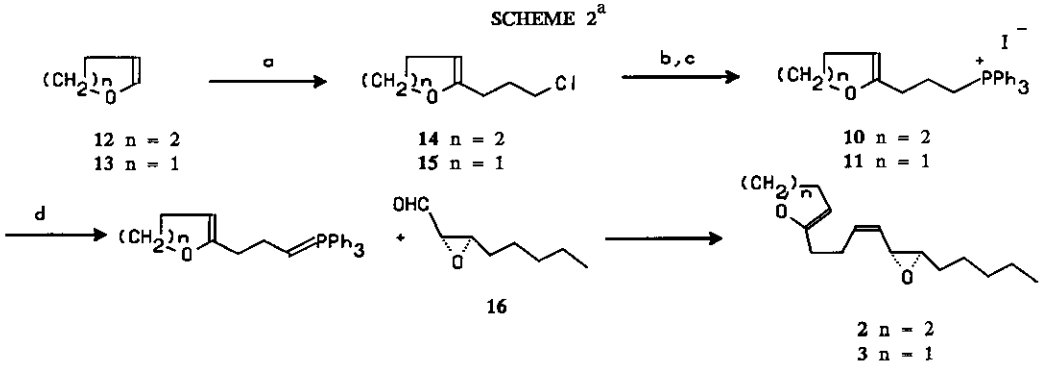
The phosphonium salts **10** and **11** were readily obtained, as outlined in Scheme 2, by metalation, and alkylation of dihydropyran **12** and dihydrofuran **13** with 1-bromo-3-chloropropane (3 equiv) to afford the chloropropyl ethers **14** and **15** (~80%).[11,12] Conversion of **14** and **15** to the respective iodides with NaI (4 equiv) in anhyd acetone in the presence of 2 equivalents of i-Pr$_2$EtN and subsequent quaternization with Ph$_3$P (1 equiv) in the presence of



(2)

i-Pr$_2$EtN (1 equiv) in anhyd CH$_3$CN at reflux (72 h) provided the salts **10** (mp 198-199°C, 57%) and **11** (mp 162-163°C, 62%) as stable, nicely crystalline materials upon trituration with hot THF.[12,13]

SCHEME 2[a]



12 n = 2
13 n = 1

14 n = 2
15 n = 1

10 n = 2
11 n = 1

16

2 n = 2
3 n = 1

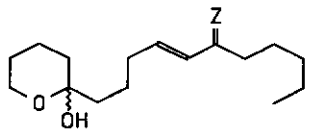
[a]**Reagents:**
a) t-BuLi (1 equiv)/ THF/ -78°C → 0°C/ 1.25 h, Cl(CH$_2$)$_3$Br (0.83 equiv)/ anhyd HMPA (0.83 equiv)/ 0°C → 25°C/ 7.33 h; b) NaI (3 equiv)/ i-Pr$_2$EtN (2 equiv)/ anhyd acetone/ Δ/ 16h; c) PPh$_3$ (1 equiv)/ i-Pr$_2$EtN (1 equiv)/ anhyd CH$_3$CN/ Δ/ 96h; d) nBuLi (1 equiv)/0°C → -20°C/ 1h, aldehyde/ -20°C → 25°C/ 2h.

Construction of the cyclization substrates **2** and **3** was completed, as shown in Scheme 2, by a kinetically-controlled Wittig reaction.[14] The ylides derived from **10** and **11** by treatment with n-BuLi (1 equiv) at 0°C in THF were condensed with the known epoxyaldehyde **16** at -20°C in THF to afford nearly exclusively (Z:E ≧96:4) the Z olefins **2** (65%) and **3** (75%) after rapid purification by filtration through florisil.[12,15] Dihydrofuran **3** is extremely sensitive to traces of acid particularly in the presence of nucleophiles, and cannot be stored or subjected to further chromatographic purification.[16] Thus, **3** was prepared and used immediately in the cyclization studies described below.

The substrates **2** ($[\alpha]_D^{30}$ = + 5.75° (c = 4, CHCl$_3$) and **3** were also readily obtained in optically active form by employing the optically active (2S,3S) epoxyaldehyde **16** ($[\alpha]_D^{23}$ = +69.7° (c = 6, CHCl$_3$)). Optically active **16** was obtained by asymmetric epoxidation of commercially available (2E) octen-1-ol in the presence of diethyl (+)-tartrate to afford (2R,3S) epoxy-1-octanol ($[\alpha]_D^{24}$ = - 9.55° (c = 2, CHCl$_3$), >90% ee) followed by oxidation with CrO$_3$-2py in CH$_2$Cl$_2$ (~40% overall yield).[17]

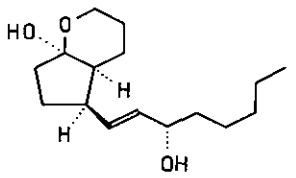
Preliminary attempts to cyclize the less sensitive dihyropyran **2** established that strong Lewis acids such as TiCl$_4$ and SnCl$_4$ were unsuitable since a variety of products were produced, and extensive decomposition/ polymerization

was observed even at relatively high dilution and at low temperatures (-78°C). Surprisingly, use of BCl_3 (1 equiv) in CH_2Cl_2 at -78°C produced, rather cleanly, a mixture of diastereomeric E allylic alcohols **17** whose gross structures were assigned on the basis of IR, NMR (400 MHz), and mass spectral data, and confirmed by oxidation of the mixture with CrO_3-2py in CH_2Cl_2 to an epimeric mixture of enones **18**.[12] Clearly, **18** can only arise as the result of isomerization of the olefinic epoxide (followed by oxidation) and addition of the elements of H_2O across the dihydropyran residue (possibly during the aqueous workup), however, no products resulting from participation of the two functional groups in the desired cyclization were observed. We hypothesized that the undesired outcome was the result of creation of a nearly full positive charge on the epoxide carbon by the strong Lewis acid (BCl_3) initiating rearrangement followed by hydration of the vinyl ether by water introduced during workup. Therefore, we turned our attention to mild silicon-based Lewis acids such $(CH_3)_3SiCl$ (TMSCl) and t-Bu$(CH_3)_2$SiCl (TBSCl) which we hoped could be prepared free of protic acid impurities in an attempt to observe the desired cyclization.[18] The cyclization studies described below utilized primarily TBSCl, since TBSCl is more easily purified and less moisture sensitive.



17 Z = OH, H

18 Z = O



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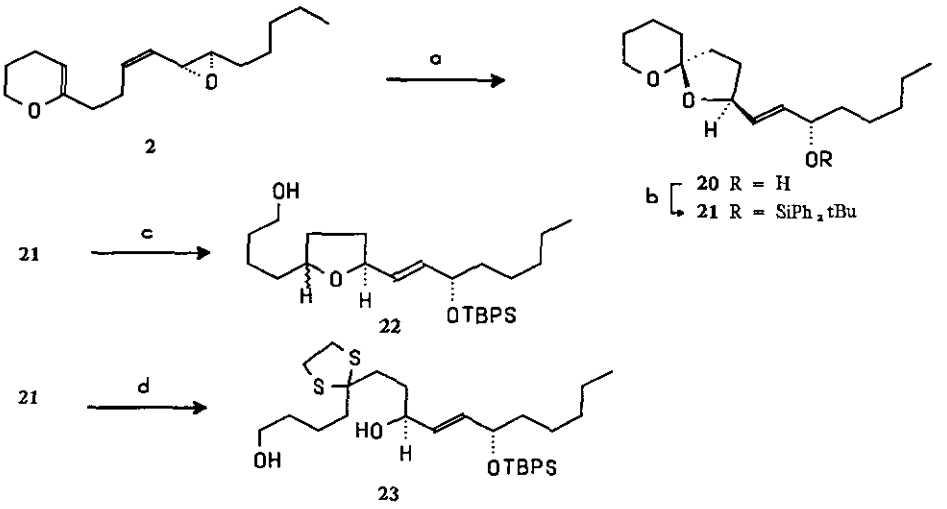
Slow addition of a solution of optically active dihydropyran **2** to a solution of pure TBSCl (1.33 equiv) in CH_2Cl_2 (0.05 M in each reactant) at 0°C resulted in immediate consumption of **2**. The reaction was quenched by addition of sat $NaHCO_3$ solution, and the crude product was purified by chromatography to afford a single polar, chromatographically homogeneous alcohol ($[\alpha]_D^{24}$ = - 1.24° (c = 3.5, $CHCl_3$)) in 75-80% yield. Surprisingly, spectroscopic analysis indicated the absence of silicon. The presence of a mass spectral parent ion at m/z 268 suggested the empirical formula $C_{16}H_{28}O_3$. *Thus, the conversion had apparently resulted in the addition of the elements of* H_2O to **2** as would be expected for the desired cyclization product. Examination of the proton NMR (400 MHz with decoupling) of the purified cyclization product established the presence of substituted tetrahydrofuran and *trans* allylic alcohol moieties. The presence of 16 signals in the ^{13}C NMR spectrum confirmed that the unknown was a single diastereomer, and the appearance of a quaternary carbon signal at δ 105.0 suggested two plausible structures, the desired hemiketal **19**, and the spirocyclic ketal **20** (Scheme 3). The latter structure, ketal **20**, whose stereochemistry *was tentatively assigned on mechanistic grounds, appeared to fit existing literature precedent somewhat better.*[12,19] However, we sought further chemical confirmation of the structure and stereochemical assignments for **20**.[20] Oxidation of **20** with CrO_3-2py in CH_2Cl_2 was inconclusive due to the formation of a variety of products, however reduction of the mono-t-butyldiphenylsilyl (TBDPS) ether **21**, obtained from **20** by treatment with t-butyldiphenylsilyl chloride (1 equiv) and imidazole (2 equiv) in DMF (room temperature, 16 h), with $NaCNBH_3$ at pH 3 (Scheme 3) provided the alcohol **22** which clearly retained the tetrahydrofuran residue as judged by NMR spectroscopy.[12] The NMR spectrum was inconsistant with a diol, the expected reduction product of **19**. Furthermore, treatment of **21** with $(CH_2SH)_2$ (10 equiv) in the presence of excess BF_3-Et_2O in CH_2Cl_2 at -60°C (1 h), conditions which have been employed previously to open hemiketals and spirocyclic ketals,[21] afforded dihydroxythioketal **23** (75%).[12] Again, production of a diol was consistant only with ketal **20**. With the gross

SCHEME 3[a]



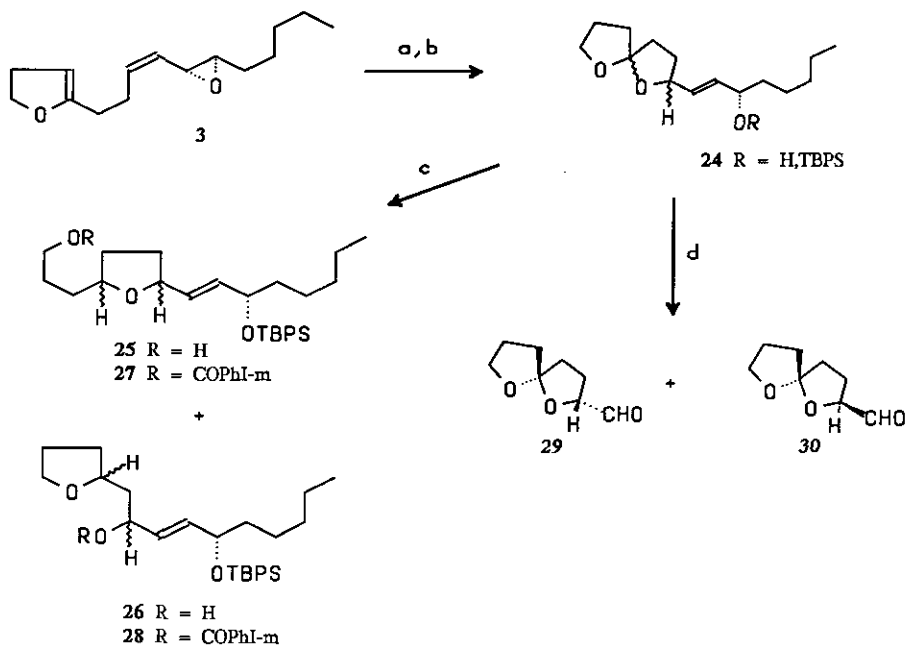
[a]Reagents:
a) TBSCl (1.25 equiv)/ CH_2Cl_2/ 0°C → 10°C/ 1.75 h; b) t-$BuPh_2SiCl$ (1.3 equiv)/imidazole (2 equiv)/ DMF/ 25°C/ 16 h; c) $NaCNBH_3$ (3 equiv)/ HCl/ aq THF/ 25°C/ 3 h; d) $(CH_2CH_2SH)_2$ (10 equiv)/ BF_3-Et_2O (catalytic)/ -60°C/ 1 h, Et_3N/ -60°C → 25°C/ 1 h.

structure of **20** confirmed, NOE experiments established the probable *cis* relationship between the methylene branch of the pyran ring and the proximal proton of the vinyl group on the tetrahydrofuran ring. These data strongly suggest that the complete stereostructure of **20** is as formulated.

A complementary study was conducted with the highly sensitive optically active dihydrofuran **3**. Treatment of **3** with TBDSCl under comparable conditions to those employed for **2** immediately produced a mixture of 4 diastereomeric alcohols **24** which were unresolvable by chromatography (~60%). However, conversion of the mixture to the corresponding TBDPS ethers, as before, followed by reduction with $NaCNBH_3$ at pH 3 afforded a mixture of two isomeric tetrahydrofurans **25** and **26** (each a diastereomeric mixture) which were separable upon conversion to the corresponding m-iodobenzoates **27** and **28**.[12] This result coupled with the presence of a signal (unresolved) at δ 114 in the ^{13}C NMR spectrum of the mixture of alcohols **24** strongly suggested that the cyclization had taken a similar course to that of **2** but with lower stereoselectivity. Final confirmation of the gross structures of **24** was obtained by ozonolysis of the related TBDPS ethers which afforded a separable mixture of diastereomeric aldehydes **29** and **30** (3:1) whose spectral characteristics, including a signal at δ 116 in the ^{13}C NMR spectrum, were identical to those reported for these substances by Ireland.[12,22]

We presume that the observed cyclization reactions are catalyzed by traces of HCl which are unavoidably present in the TBDSCl. When combined with moisture present in the reaction medium or introduced during the aqueous workup and purification, the HCl induces rapid hydration of the endocyclic vinyl ether double bond in **2** and **3** followed by intramolecular ether formation in an S_N2' manner leading to the spiroketals **20** and **24**. The production of a single diastereomer in the case of **20** is most likely ascribable to the influence of the anomeric effect in the lactol intermediate and the correspondingly greater steric demands of the six-membered ring in the subsequent cyclization. However, we have no experimental evidence which requires the foregoing sequence of events during the cyclization.

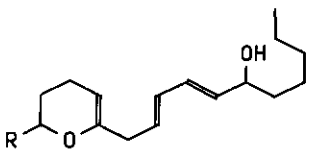
SCHEME 4[a]



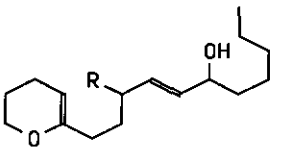
[a]**Reagents:**
a) TBSCl (1 equiv)/ CH_2Cl_2/ 0°C/ 40 min, sat $NaHCO_3$/ 0°C; b) $tBuPh_2SiOTf$ (1equiv)/ lutidine (2 equiv)/ CH_2Cl_2/ -78°C → 25°C/ 1.5 h, 10% aq $NaHCO_3$; c) $NaCNBH_3$ (3 equiv)/ HCl/ aq THF/ 25°C/ 3 h, m-IPhCOCl (1 equiv)/ pyridine/ 25°C/ 12 h; d) O_3 (xs)/ CH_2Cl_2-CH_3OH (3:1)/ -78°C/ 30 min, DMS/ -78°C → 25°C/ 2h.

In an effort to avoid the intervention of acid catalyzed processes, and to potentially alleviate stereoelectronic problems which may well be the root cause of our failure to observe participation of the vinyl ether bond in the desired carbocyclization,[23] we examined the use of Pd(0) catalysis. Use of π-allyl palladium intermediates in ring forming reactions was pioneered by Trost,[24] and has been exploited by a number of other groups.[25] The expected stereochemical outcome with respect to the vinyl epoxide unit should result in the required overall SYN selectivity.[24,25]

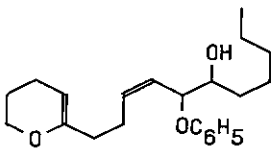
Treatment of (∓) **3** with a catalytic amount of $Pd(PPh_3)_4$[25] in the absence of an external nucleophile resulted in apparent formation of the required π-allyl palladium intermediate, however, proton transfer occurred in preference to participation of the vinyl ether double bond affording dienol **31** (E,E/ Z,E mixture) in 95% yield.[12] Even more remarkably, when phenol was introduced to quench the alkoxide, a mixture (7:1) of 1,4 and 1,2 addition products **32** and **33** was obtained.[12] The products of 1,2 addition, such as **33**, are rarely if ever observed with olefinic epoxides.[24] Use of the sterically hindered and effectively nonnucleophilic 2,6-di-t-butyl-4-methylphenol only resulted in the formation of the previously observed product of elimination, dienol **31**. To further assure ourselves that the required π-allyl palladium species was formed, (∓) **3** was treated with $Pd(PPh_3)_4$ (cat) and dimethyl malonate in THF (70°C, 5min) to afford the expected bimolecular addition product **34** (~60%). We reasoned that enhancing the nucleophilicity of the vinyl ether bond might overcome the reluctance to participate in ring closure. Therefore, we prepared the methoxydihydropyran **35** by a route analogous to that for **3** (Scheme 2).[12] Unfortunately, the identical pattern of reactivity was observed for **35**. Exposure of **35** to $Pd(PPh_3)_4$ (cat) in THF at 65°C afforded, in this case, only the E,E dienol **36**.



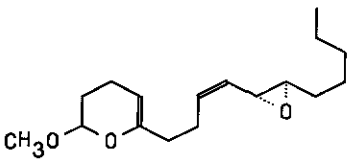
31 R = H (E,E + Z,E)
36 R = OCH_3 (E,E only)



32 R = OC_6H_5
34 R = $CH(CO_2CH_3)_2$



33



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The failure of all the substrates examined to undergo carbocyclization by participation of the endocyclic vinyl ether double bond is probably the result of stereoelectronic factors.[2,4] While the cationic cyclizations of the type desired (Eq 1) do not strictly fit into the categories discussed by Baldwin,[2,3] it is clear that the required orbital overlap for the double bond participation to form a five-membered ring does result in introduction of some strain. However, the results of our earlier cyclization studies,[2,3] and examination of molecular models of the required transition state geometry do not suggest that orbital overlap would be sufficiently poor to preclude cyclization. This conclusion would be particularly valid for the palladium catalyzed reactions. In these cases, the vinyl ether double bond may simply be too weakly nucleophilic to attack the π-allyl palladium intermediate even when the reaction is intramolecular.[2,7]

Additional studies of the carbocyclization of substrates such as **2** and **3** by means of radical intermediates are presently in progress, and the results will be reported in due course.

ACKNOWLEDGMENTS

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10. Deuterium quenching studies unequivocally showed deprotonation to have occurred at the para methyl group of the tosylate.

11. The route is readily adaptable to the production of optically active materials, since the epoxyaldehyde precursor is presumably available in optically active form of the correct absolute configuration for conversion to the natural prostaglandins by asymmetric epoxidation of the related allylic alcohol.[17]

12. All the new compounds exhibited IR, NMR (400 MHz) and high resolution mass spectral or combustion analytical data consistent with assigned structures.
Partial NMR spectal data:

2: δ 5.67 (dt, J_1 = 12 Hz, J_2 = 6 Hz, 1H), 5.07 (t, J = 9 Hz, 1H), 4.50 (s(br), 1H), 3.98 (t, J = 3 Hz, 2H), 3.35 (d, J = 9 Hz, 1H), 2.82 (m, 1H), 2.38 (m, 2H), 2.10 (t, J = 6 Hz, 2H), 1.98 (m, 2H), 1.78 (t, J = 3 Hz, 2H), 1.56 (t, J = 3 Hz, 2H), 1.32 (m, 6H), 0.90 (s(br), 3H);

3: δ 5.73 (dt, J_1 = 9 Hz, J_2 = 6 Hz, 1H), 5.13 (t, J = 8 Hz, 1H), 4.67 (s(br), 1H), 4.35 (t, J = 10 Hz, 2H), 3.39 (d, J = 9 Hz, 1H), 2.85 (m, 1H), 2.63 (m, 2H), 2.43 (m, 2H), 2.23 (t, J = 6 Hz, 4H), 1.57 (t, J = 6 Hz, 2H), 1.27 (m, 4H), 0.90 (t, J = 3 Hz, 3H);

10: δ (90 MHz) 7.75 (m, 15H), 4.50 (s(br), 1H), 3.93 (t, J= 7 Hz, 2H), 3.65 (m, 2H), 1.85 (m, 8H);

14: δ (90 MHz) 4.50 (t, J = 2.5 Hz, 1H), 3.93 (t, J = 7 Hz, 2H), 3.53 (t, J = 7 Hz, 2H), 1.94 (m, 8H);

18: δ 6.77 (m, 1H), 6.25 (m, 1H), 4.68 (m, 1H), 3.88 (m, 1H), 3.64 (t, J = 13 Hz, 1H), 2.55 (t, J = 8 Hz, 2H), 2.33 (m, 1H), 2.18-1.50 (m, 13H), 1.31 (m, 4H), 0.93 (t, J = 7 Hz, 3H);

20: δ 5.68 (m, 2H), 4.50 (m, 1H), 4.15 (m, 1H), 3.87 (dt, J_1 = 6 Hz, J_2 = 2 Hz, 1H), 3.60 (s(br), 1H), 2.20 (m, 1H), 2.05 (m, 1H), 1.75 (m, 11H), 1.30 (m, 6H), 0.95 (t, J = 3 Hz, 3H);

23: δ 7.70 (m, 5H), 7.35 (m, 5H), 5.40 (m, 2H), 4.18 (m, 1H), 3.65 (m, 2H), 3.25 (t, J = 2 Hz, 4H), 2.20 (m, 1H), 2.05 (m, 1H), 1.95 (m, 2H), 1.60 (m, 8H), 1.35 (m, 8H), 1.05 (s(br), 9H), 0.90 (t, J = 2 Hz, 3H);

27: δ 8.35 (m, 1H), 8.00 (m, 1H), 7.85 (d, J = 7 Hz, 1H), 7.60 (m, 4H), 7.30 (m, 6H), 7.15 (t, J = 7 Hz, 1H), 5.55 (m, 2H), 5.40 (m, 1H), 5.25 (m, 1H), 4.30 (m, 3H), 4.10 (m, 1H), 3.55 (m, 1H), 2.00 - 1.70 (m, 2H), 1.60 - 1.30 (m, 8H), 1.25 - 1.05 (s, 9H), 0.80 (t, J = 6 Hz, 3H);

29: δ 9.60 (s, 1H), 4.30 (dt, J_1 = 9 Hz, J_2 = 3 Hz, 1H), 3.90 (m, 2H), 2.20 - 1.80 (m, 8H;
δ (^{13}C) 204.3, 116.6, 82.5, 67.4, 34.3, 33.7, 26.3, 24.5;

31: δ 6.50 (m, 1H), 6.10 (m, 2H), 5.70 (m, 2H), 5.50 (m, 1H), 4.50 (s, 1H), 4.10 (m, 1H), 4.00 (t, J = 4 Hz, 2H), 2.90 (dd, J_1 = 9 Hz, J_2 = 1 Hz, 1H), 2.80 (dd, J_1 = 9 Hz, J_2 = 1 Hz, 1H), 2.00 (m,2H), 1.60 - 1.30 (m, 8H), 0.90 (m, 3H);

32: δ 7.25 (m, 2H), 6.90 (m, 3H), 5.70 (t, J = 4 Hz, 2H), 4.65 (m, 1H), 4.50 (m, 1H), 4.10 (m, 1H), 4.00 (m, 2H), 2.20 - 1.10 (m, 16H), 0.90 (m, 3H);

33: δ 7.30 (m, 2H), 6.90 (m, 3H), 5.80 (m, 2H), 5.50 (dd, J_1 = 12 Hz, J_2 = 7 Hz, 1H), 5.25 (s, 1H), 4.50 (m, 1H), 4.40 (m, 1H), 3.95 (t, J = 3 Hz, 2H), 3.80 (m, 1H), 2.30 (m, 3H), 2.10 - 1.30 (m, 16H), 0.90 (m, 3H);

35: δ 5.70 (m, 1H), 5.10 (t, J = 9 Hz, 1H), 4.95 (t, J = 2 Hz, 1H), 4.60 (m, 1H), 3.50 (s, 3H), 3.40 (dd, J_1 = 9 Hz, J_2 = 1 Hz, 1H), 2.80 (m, 1H), 2.60 - 2.30 (m, 2H), 2.20 - 1.30 (m, 14H), 0.90 (m, 3H);

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