the carboxylate ion should be very pronounced in a reaction with a positively charged catalyst such as H_3O^+. In the reaction between the carboxylate form of **3a** and a neutral catalyst (such as CH_3COOH), this stabilizing effect is of minor importance, in agreement with the observation.

The results obtained for both the *Z* isomer (**3**) and the *E* isomer (**4**) have been confirmed by Kresge in the kinetic investigation of **1** and its *E* isomer, where it was shown that **1** follows the same kinetic pattern that has been found in the present investigation of the model compound of **1**.[14]

Acknowledgment. We express our thanks to Professor A. J. Kresge, University of Toronto, for equipment placed at our disposal during a stay of T.H. at the University of Toronto. We are grateful to the Swedish Natural Science Research Council for financial support of this work.

Supplementary Material Available: Rate data for the hydrolyses of (*Z*)- and (*E*)-1-(3-carboxyphenyl)-2,5-epoxypent-1-ene and the corresponding methyl esters in various solutions (Tables S1–S8) (26 pages). Ordering information is given on any current masthead page.

Kinetics of Hydrolysis of the Vinyl Ether Functional Group of the Stable, Bioactive Prostacyclin Analogue Taprostene (CG 4203)

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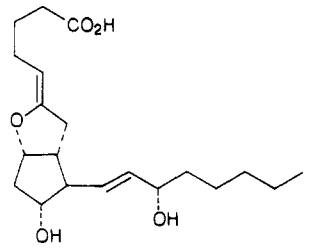
Rates of hydrolysis of the vinyl ether functional groups of the stable, bioactive prostacyclin analogue taprostene [(5*Z*,13*E*,9α,11α,15*S*)-2,3,4-trinor-1,5-*inter*-*m*-phenylene-6,9-epoxy-11,15-dihydroxy-15-cyclohexyl-16,17,18,19,20-pentanor]prosta-5,13-dienoic acid (**2**) (CG 4203), its methyl ester **3**, and its 5*E* isomer **4** were measured in dilute aqueous perchloric acid solutions and also in formic acid, acetic acid, and biphosphate ion buffers at 25 °C, ionic strength = 0.10 M. These data provide rate profiles that show that the two acids, **2** and **4**, are each about 3 times more reactive in their ionized, carboxylate forms than in their carboxylic acid forms. Rate constants for all three substrates are normal for vinyl ethers of this structure, and pK_a's of the acids **2** and **4** are consistent with expectation for aromatic carboxylic acids. The lifetime of **2** at physiological pH is 9 days.

Prostacyclin, **1**, is a naturally occurring bioregulator with remarkable physiological properties: it is the most potent inhibitor of blood-clot formation so far known.[1] Unfortunately, prostacyclin is also very unstable: its lifetime at physiological pH (=7) is only 3 min.[2] We have recently traced this instability to hydrolysis of prostacyclin's vinyl ether group accelerated 100-fold through intramolecular general-acid catalysis by the molecule's carboxylic acid function.[3]



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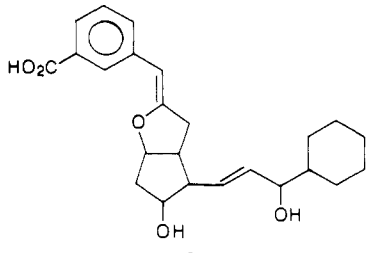
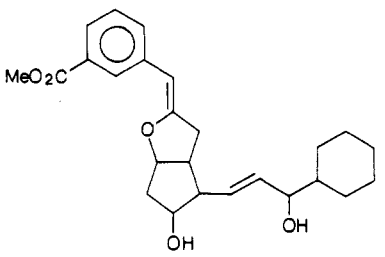
The hydrolysis of vinyl ethers is known to be inhibited by β-phenyl substituents,[4] such as that present in the recently prepared bioactive prostacyclin analogue taprostene, **2** (CG 4203).[5] The carboxylic acid group of this substance, moreover, is situated in a position from which intramolecular catalysis is not possible. This substance should therefore be much more stable than prostacyclin, and a hydrolytic lifetime of 20 days at physiological pH has in fact been predicted for it.[6] We now present evidence that substantiates this prediction.



2

Experimental Section

Materials. **2** {[(5*Z*,13*E*,9α,11α,15*S*)-2,3,4-trinor-1,5-*inter*-*m*-phenylene-6,9-epoxy-11,15-dihydroxy-15-cyclohexyl-16,17,18,19,20-pentanor]prosta-5,13-dienoic acid}, its methyl ester (**3**), and its 5*E* isomer (**4**), are substances whose synthesis has been



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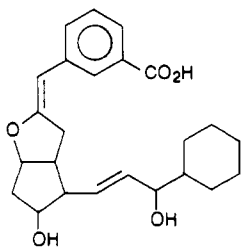

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[†] University of Toronto.
[‡] Grünenthal GmbH.

(1) For recent reviews of the physiological and chemical properties of prostacyclin, see: Bartman, W.; Beck, G. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 751–764. Nelson, N. A.; Kelly, R. C.; Johnson, R. A. *Chem. Eng. News* **1982**, *60*(30) 30–44.

(2) Cho, M. J.; Allen, M. A. *Prostaglandins* **1978**, *15*, 943–954. Chiang, Y.; Kresge, A. J.; Cho, M. J. *J. Chem. Soc., Chem. Commun.* **1979**, 129–130.

(3) (a) Chiang, Y.; Cho, M. J.; Euser, B. A.; Kresge, A. J. *J. Am. Chem. Soc.* **1986**, *108*, 4192–4196. (b) Bergman, N. A.; Chiang, Y.; Jansson, M.; Kresge, A. J.; Ya, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1366–1368.

(4) (a) Kresge, A. J.; Chen, H. J. *J. Am. Chem. Soc.* **1972**, *94*, 2818–2822. (b) Chiang, Y.; Kresge, A. J.; Young, C. I. *Can. J. Chem.* **1978**, *56*, 461–464.

(5) Flohé, L.; Bohlke, H.; Frankus, E.; Kim, S.-M.A.; Lintz, W.; Loschen, G.; Michel, G.; Muller, B.; Schneider, J.; Seipp, U.; Vollenberg, W.; Wilsmann, K. *Arzneim.-Forsch.* **1983**, *33*(II), 1240–1248.

(6) Kresge, A. J. *Acc. Chem. Res.* **1987**, *20*, 364–370.

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described.[5] The acids **2** and **4** were used as their sodium salts. HPLC analysis showed the sample of **2** (sodium salt) used here to be 98.8% pure, with **4** (sodium salt) as the probable impurity; the sample of **4** (sodium salt) to be 94.7% pure, with **2** (sodium salt) as the probable impurity; and the sample of **3** to be 99.3% pure.

All other materials were best available commerical grades. Solutions were prepared with deionized water purified further by distillation.

Kinetics. Rates of hydrolysis were determined spectrophotometrically by monitoring the decrease in the strong absorbance of the styrene-type chromophore of **2**, **3**, and **4** at $\lambda \cong 275$ nm. Measurements were made with a Cary 118 spectrometer whose cell compartment was thermostated at 25.0 ± 0.05 °C. The kinetic data conformed to the first-order rate law well, and observed first-order rate constants were evaluated by standard methods.

pK_a Determinations. Acid dissociation constants of the carboxylic acid groups of **2** and **4** were determined spectrophotometrically by utilizing the fact that the carboxylate forms of both substrates absorb more strongly at low wavelengths than do the carboxylic acid forms. Some hydrolysis of the vinyl ether groups of these substrates occurred during these determinations, but the need to correct for this was obviated by making absorbance measurements at an isosbestic point of the hydrolysis reaction, $\lambda = 211$ nm. Ionic strength was maintained constant at 0.10 M by adding NaCl as required. Concentration dissociation constants at this ionic strength, Q_a, were calculated by using eq 1, in which

$$Q_a = [H^+](A - A_{HA})/(A_{A^-} - A) \quad (1)$$

A_{HA} and A_{A^-} are the limiting absorbances of the carboxylic acid and carboxylate forms measured in 2×10^{-3} M $HClO_4$ and $H_2PO_4^-/HPO_4^{2-}$ buffer ($[H_2PO_4^-]/[HPO_4^{2-}] = 2$) solutions, respectively, and A is the absorbance measured at intermediate acidities in HCO_2H and CH_3CO_2H buffers. The data fit this expression well.

Results

Kinetics. Rates of hydrolysis of the vinyl ether functional groups of **2**, **3**, and **4** were determined in dilute perchloric acid solutions (0.02–0.002 M) and also in formic acid, acetic acid, and biphosphate ion buffers. All measurements were made in wholly aqueous medium at 25 °C and ionic strength = 0.10 M. These data are summarized in Tables S1 and S2.[7]

The hydrolysis of vinyl ethers is expected to show general-acid catalysis, and marked buffer catalysis was in fact observed in all of the buffers used. The data, which consisted of sets of runs performed in series of solutions at constant buffer ratio and therefore constant $[H^+]$,[8] were consequently fitted to eq 2 by linear least-squares analysis,

$$k_{obsd} = (k_{H^+})_{eff}[H^+] + (k_{HA})_{eff}[HA] \quad (2)$$

and values of effective hydronium ion and general-acid catalytic coefficients were thus obtained.

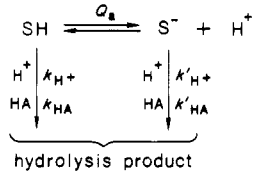
In the case of ester **3**, $(k_{HA})_{eff}$ for a given buffer acid proved to be invariant upon changes in buffer ratio, and $(k_{H^+})_{eff}$ for all buffers was consistent with the hydronium ion catalytic coefficient that could be calculated from the perchloric acid data. This substrate thus provided an uncomplicated example of simple general-acid catalysis. Least-squares analysis of the relationship between log $[H^+]$ and the logarithms of all values of $(k_{H^+})_{eff}$ plus the k_{obsd} determined in perchloric acid solutions gave a good linear correlation with unit slope: $\log k = 0.696 \pm 0.011 + (1.000 \pm 0.004) \log [H^+]$; the intercept corresponds to $k_{H^+} = 4.97 \pm 0.12$ M^{-1} s^{-1}. A somewhat more precise value of this catalytic coefficient, $k_{H^+} = 4.85 \pm 0.06$ M^{-1} s^{-1}, could be obtained from least-squares analysis of the nonlogarithmic, linear relationship between $[H^+]$ and $(k_{H^+})_{eff}$ plus k_{obsd} from the perchloric acid solutions.

Table I. Summary of Rate Constants for Hydrolysis of the Vinyl Ether Groups of Prostacyclin Analogues in Aqueous Solution (T = 25 °C, Ionic Strength = 0.10 M)

	$k/(M^{-1}\ s^{-1})$				
	2		3	4	
cat.	RCO_2H	RCO_2^-	RCO_2Me	RCO_2H	RCO_2^-
H^+	4.92	13	4.85	2.56	7.8
HCO_2H	0.032		0.027	0.019	
CH_3CO_2H	0.0067	0.0085	0.0059	0.0035	0.0057
$H_2PO_4^-$					0.00039

Formic and acetic acid catalytic coefficients for hydrolysis of the vinyl ether group of this substrate (**3**), obtained as slopes in the relationship of eq 2, are listed in Table I. They provide the Brønsted exponent $\alpha = 0.66$. This is nicely consistent with $\alpha = 0.70$ for the simple β-phenyl-substituted vinyl ether PhCH=C(OMe)Me, which has closely similar reactivity;[9] the present result also differs in the expected direction from $\alpha = 0.58$ for the considerably more reactive methyl ester of prostacyclin itself.[3a]

The carboxylic acid substrates **2** and **4** showed somewhat more complicated catalytic behavior. For these substances, $(k_{HA})_{eff}$ increased systematically with increasing pH in the formic acid acetic acid buffers, and $(k_{H^+})_{eff}$ was greater in these solutions than the hydronium ion catalytic coefficients that could be calculated from the perchloric acid data. This behavior suggests that these substrates are undergoing ionization to their carboxylate forms and that this change enhances the reactivity of their vinyl ether groups. The reaction scheme that applies to a situation such as this is shown in eq 3, in which SH and S^- denote



the carboxylic acid and carboxylate forms of the substrate, respectively, Q_a is the concentration dissociation constant that governs the ionization of SH at the relevant ionic strength, and unprimed rate constants refer to the reactions of SH and primed, to the reactions of S^-. The rate law governing this scheme is given as eq 4.

$$k_{obsd} = \frac{(k_{H^+}[H^+] + k'_{H^+}Q_a)[H^+] + (k_{HA}[H^+] + k'_{HA}Q_a)[HA]}{[H^+] + Q_a} \quad (4)$$

The first two terms of this rate law refer to catalysis by H^+; they are equivalent to the first term of eq 2. The data corresponding to this part of the rate law for substrates **2** and **4** are plotted as the rate profiles of Figure 1. The solid lines shown there were calculated with parameters (k_{H^+}, k'_{H^+}, and Q_a) obtained by least-squares analysis; it is evident that the data fit the expected relationship well.

(7) Supplementary material; see paragraph at end of paper regarding availability.

(8) In some of the more acidic formic acid buffers, $[H^+]$ was not quite constant along a series of solutions with constant stoichiometric buffer ratio. Such "buffer failure"[9] was corrected for by adjusting observed rate constants to a common hydronium ion rate contribution, $(k_{H^+})_{eff}[H^+]$, for the series using values of $(k_{H^+})_{eff}$ estimated from the rate profiles; these adjustments never amounted to more than a few percent of k_{obsd}. Hydronium ion concentrations needed for this purpose were obtained by calculation using literature pK_a's for the buffer acids and activity coefficients recommended by Bates.[10]

(9) Keeffe, J. R.; Kresge, A. J. "Investigations of Rates and Mechanisms of Reactions". In *Techniques of Chemistry*; Bernasconi, C. F., Ed.; Wiley: New York, 1986; Vol. 6, Part 1, Chapter XI.

(10) Bates, R. G., *Determination of pH. Theory and Practice*; Wiley: New York, 1973; p 49.

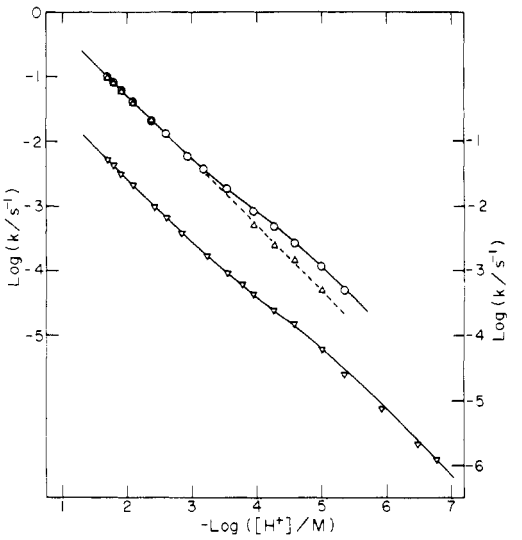


Figure 1. Rate profiles for hydrolysis of the vinyl ether groups of **2** (○), **3** (△), and **4** (▽) in aqueous solution at 25 °C. The vertical scale for **4** (right ordinate) is offset from that for **2** and **3** (left ordinate) by one log unit.

The results are $k_{H^+} = 4.92 \pm 0.03\ M^{-1}\ s^{-1}$, $k'_{H^+} = 12.7 \pm 3.4\ M^{-1}\ s^{-1}$, and $Q_a = (6.4 \pm 4.3) \times 10^{-5}$ M for **2**; and $k_{H^+} = 2.56 \pm 0.02\ M^{-1}\ s^{-1}$, $k'_{H^+} = 7.78 \pm 3.52\ M^{-1}\ s^{-1}$, and $Q_a = (2.89 \pm 2.73) \times 10^{-5}$ M for **4**. Because the two limiting straight-line portions of these rate profiles are not displaced very far from one another, i.e., because k'_{H^+} is not much greater than k_{H^+}, these experiments provide only approximate values of Q_a; the results obtained, however, are consistent with expectation for carboxylic acids of this structure and agree with the more precisely measured values described below.

The second two terms of the rate law of eq 4 pertain to catalysis by the undissociated buffer acids HA. They predict that $\Delta k_{obsd}/\Delta[HA]$ ($=(k_{HA})_{eff}$) multiplied by ($[H^+] + Q_a$) will be a linear function of $[H^+]$ with k_{HA} as the slope and $k'_{HA}Q_a$ as the intercept (eq 5). This was generally

$$\frac{\Delta k_{obsd}}{\Delta[HA]} = (k_{HA})_{eff} = \frac{k_{HA}[H^+] + k'_{HA}Q_a}{[H^+] + Q_a} \qquad (5)$$

found to be the case; Figure 2 shows such a plot for the reaction of **2** in acetic acid buffers. Only in acetic acid buffers, however, could both k_{HA} and k'_{HA} be evaluated well: in formic acid buffers, the intercepts of such plots were too small to define k'_{HA}, and in biphosphate buffers, the slopes were too small to define k_{HA}; this reflects the fact that in formic acid buffers the substrates existed largely in their carboxylic acid forms and most of the hydrolysis reaction went through this species, whereas in biphosphate buffers they existed largely in the carboxylate forms and most of the reaction went through that species.

The buffer acid catalytic coefficients evaluated in this way are listed in Table I. The formic and acetic acid data give $\alpha = 0.68$ for **2** and $\alpha = 0.73$ for **4**, both of which are consistent with the result for **3** as well as with α values for the hydrolysis of vinyl ether groups in general.

pK_a Determinations. Ionization constants of the carboxylic acid groups of **2** and **4** were determined by making absorbance measurements on solutions of the partly ionized substrates in formic and acetic acid buffers of various hydrogen ion concentrations. Ten to fifteen measurements were made on each substrate; these data are summarized in Table S3.[7]

These measurements were performed at a constant ionic strength of 0.10 M. They provided the concentration

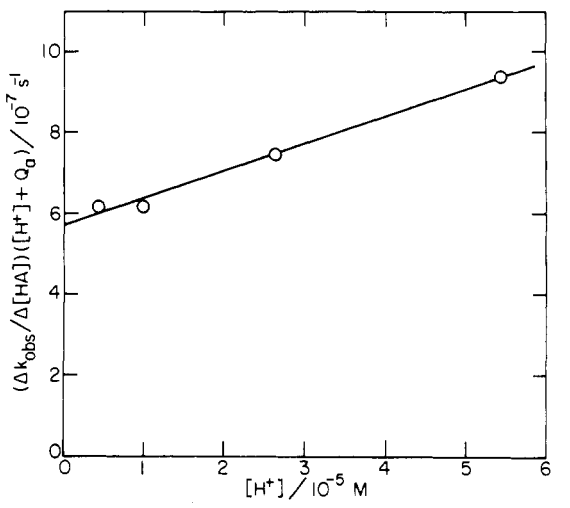


Figure 2. Relationship between $[H^+]$ and effective buffer-dependent rate constants, $(k_{HA})_{eff}$, for hydrolysis of the vinyl ether group of **2** in aqueous acetic acid buffer solutions at 25 °C.

dissociation constants $Q_a = (6.75 \pm 1.45) \times 10^{-5}$ M for **2** and $Q_a = (6.52 \pm 1.20) \times 10^{-5}$ M for **4**. These results may be converted to thermodynamic acid dissociation constants referred to infinitely dilute solution standard states by application of appropriate activity coefficients;[10] this gives p$K_a = 4.35 \pm 0.09$ for **2** and p$K_a = 4.36 \pm 0.08$ for **4**. Both of these values are consistent with expectation for acids of this structure; e.g., p$K_a = 4.20$ for benzoic acid.

Discussion

Rate Profiles. Of the three substances investigated here, the simplest rate profile is given by **3**, the substrate in which the carboxylic acid group has been converted to a methyl ester. This log–log rate profile (Figure 1) consists of a single straight line with exactly unit slope, which means that a single hydronium ion catalytic coefficient controls the rate of the hydronium ion catalyzed reaction over the entire pH range. This is the behavior expected for the hydrolysis of a vinyl ether with no ionizable or potentially catalytic functional groups that might alter the reaction mechanism; it is entirely consistent with expectation for a molecule such as **3**.

The remaining two substrates give more complex rate profiles. As Figure 1 shows, both consist of two straight-line portions, each of unit slope, joined by short intermediate regions; and in each case the shift from one straight line to the other may be attributed to ionization of the carboxylic acid groups that these substrates contain. This is reminiscent of the behavior of prostacyclin,[3a] but there is a very important difference: in the hydrolysis of prostacyclin the displacement of the two straight-line portions corresponds to a 100-fold rate acceleration, but for the present substrates the acceleration is only a factor of 3. This is significant because the acceleration in the case of prostacyclin may be attributed to intramolecular general-acid catalysis by that molecule's carboxylic acid group, whereas the carboxylic acid groups in the present substrates are located in positions from which such intramolecular catalysis is not possible.

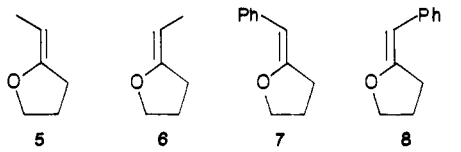
The modest accelerations found here can, however, be attributed to electrostatic effects. The rate-determining step in vinyl ether hydrolysis is known to be proton transfer from the catalyzing acid to the substrate, eq 6.[12]

$$HA + CH_2{=}CHOR \rightarrow A^- + CH_3CHOR^+ \qquad (6)$$

This is a process that puts positive charge on the substrate, and that positive charge can be stabilized by Coulombic interaction with a negative charge in sufficiently close proximity. Conversion of a carboxylic acid to a carboxylate group at the meta position of a β-phenyl substituent, such as occurs in the acid ionization of **2** or **4**, should therefore accelerate the rate of the vinyl ether hydrolysis reaction. The effect, moreover, can be expected to be greater for proton transfer from positively charged acid catalysts, such as H_3O^+, than from uncharged catalysts such as RCO_2H, as is observed here: the rate accelerations given by the present data for H_3O^+ catalysis are $k'_{H^+}/k_{H^+} = 2.6 \pm 0.7$ for **2** and $k'_{H^+}/k_{H^+} = 3.0 \pm 1.4$ for **4**, whereas those for CH_3CO_2H catalysis are $k'_{HA}/k_{HA} = 1.3 \pm 0.1$ for **2** and $k'_{HA}/k_{HA} = 1.6 \pm 0.1$ for **4**. Electrostatic effects similar to these have been observed for other vinyl ether hydrolysis reactions.[13]

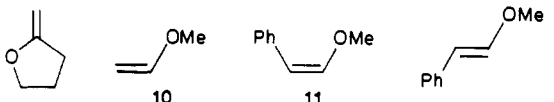
Reactivity. The present rate measurements give the prostacyclin analogue **2** a hydrolytic lifetime at physiological pH of 9 days. This is half as long as the prediction of 20 days,[6] but that estimate was made without knowledge of the electrostatic effect discovered here, which shortens the lifetime by a factor of 2.6. At any rate, a lifetime of 9 days is certainly adequate for any therapeutic or other biomedical application.

The trans isomer **4** is less reactive than **2** by a factor of about 2. Such a difference between cis and trans isomers is usually observed in vinyl ether hydrolysis; for example, for the isomeric 2-ethylidenetetrahydrofurans **5** and **6**, whose vinyl ether ring system is closely similar to that of **2** and **4**, $k_{H^+} = 640\ M^{-1}\ s^{-1}$ for **5** and $k_{H^+} = 290\ M^{-1}\ s^{-1}$ for **6**.[14] This could be the result of initial-state energy differences: ab initio calculations suggest that the π-electronic systems of trans vinyl ethers are slightly more stable than those of the cis isomers;[15] such differences would of course be lost upon protonation of the vinyl ether double bond, and that would lead to more rapid hydrolysis reactions for the cis compounds.



5 6 7 8

It is instructive to predict the reactivities of the styrylidene derivatives of tetrahydrofuran, **7** and **8**. This may be done by applying to $k_{H^+} = 3.3 \times 10^3\ M^{-1}\ s^{-1}$ for 2-methylenetetrahydrofuran (**9**)[14] the factors by which β-phenyl substitution retards vinyl ether hydrolysis, as obtained, for example, by a comparison of $k_{H^+} = 0.76\ M^{-1}\ s^{-1}$ for methyl vinyl ether[12b] with $k_{H^+} = 2.7 \times 10^{-3}\ M^{-1}\ s^{-1}$ and $7.0 \times 10^{-4}\ M^{-1}\ s^{-1}$ for the cis and trans isomers of β-methoxystyrene (**11** and **12**).[4b] Such a treatment gives $k_{H^+} = 12\ M^{-1}\ s^{-1}$ for **11**, in reasonable agreement with $k_{H^+} = 4.9\ M^{-1}\ s^{-1}$ measured here for the cis substrate **2**, and $k_{H^+} = 3.0\ M^{-1}\ s^{-1}$ for **12**, in remarkably good agreement with $k_{H^+} = 2.6\ M^{-1}\ s^{-1}$ measured here for the trans substrate **4**. This good accord between measured and expected values serves to underscore the fact that the prostacyclin analogues investigated here are entirely normal in their vinyl ether reactivity.



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Supplementary Material Available: Tables of rate and equilibrium data (9 pages). Ordering information is given on any current masthead page.

(11) Kresge, A. J.; Chen, H. J. *J. Am. Chem. Soc.* **1972**, *94*, 2818–2822.
(12) (a) Salomaa, P.; Kankaanpera, A.; Lajunen, M. *Acta Chem. Scand.* **1966**, *20*, 1790–1801. Kresge, A. J.; Chiang, Y. *J. Chem. Soc. B* **1967**, 53–57, 58–61. Kresge, A. J.; Chen, H. L.; Chiang, Y.; Murrill, E.; Payne, M. A.; Sagatys, D. S. *J. Am. Chem. Soc.* **1971**, *93*, 413–423. (b) Kresge, A. J.; Sagatys, D. S.; Chen, H. L. *J. Am. Chem. Soc.* **1977**, *99*, 7228–7233. (c) Burt, R. A.; Chiang, Y.; Chwang, W. K.; Kresge, A. J.; Okuyama, T.; Tang, Y. S.; Yin, Y. *J. Am. Chem. Soc.* **1987**, *109*, 3787–3788. Okuyama, T.; Fueno, T.; Nakatsuji, H.; Furukawa, J. *J. Am. Chem. Soc.* **1967**, *89*, 5826–5831. Kreevoy, M. M.; Eliason, R. E. *J. Phys. Chem.* **1968**, *72*, 1313–1316.
(13) Kresge, A. J.; Chiang, Y. *J. Am. Chem. Soc.* **1973**, *95*, 803–806. Chwang, W. K.; Eliason, R.; Kresge, A. J. *J. Am. Chem. Soc.* **1977**, *99*, 805–808. Loudon, G. M.; Smith, C. K.; Zimmerman, S. E. *J. Am. Chem. Soc.* **1974**, *96*, 465–479. Loudon, G. M.; Ryono, D. E. *J. Am. Chem. Soc.* **1976**, *98*, 1900–1907.
(14) Taskinen, E. *Ann. Acad. Sci. Fenn., Ser. A* **1972**, *163*, 1–64.
(15) Okuyama, T., personal communication.

Exploration of a Novel Cyclization Reaction. A Synthesis of (±)-β-Eudesmol

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An attempt was made to develop a variation of the Lewis acid catalyzed addition of trimethylsilyl enol ethers to ketals in which carbon–carbon bond formation occurs at one of the alcohol carbon atoms rather than at the ketal carbon. Specifically, a variety of conditions was employed in an unsuccessful effort to cause ketal **3**, prepared by conjugate addition of **12** to **8**, to cyclize to **4**, which was to be converted to **5**, a known precursor of β-eudesmol (**6**). In a related but more conventional approach to such a cyclization, ditosylate **20**, which, like **3**, has a prochiral carbon in its side chain, was cyclized diastereoselectively to the 7β-substituted **25**, which was readily converted to **5**.

The Lewis acid catalyzed addition of trimethylsilyl enol ethers to ketals (Mukaiyama reaction) has found widespread use in organic synthesis.[1] In all reported cases carbon–carbon bond formation occurs at the ketal carbon,

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