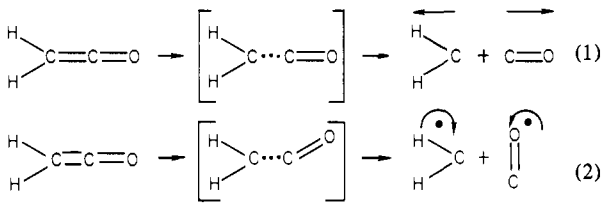
and filled with CO ($p_{CGF} \geq 15$ torr).

Under conditions where rotational relaxation is complete, measurements of the CO fluorescence intensity transmitted through an evacuated (I_0) and filled (I_{CGF}) CGF cell allow the extent of vibrational excitation in the photofragment to be characterized in terms of a vibrational temperature,[15] T_v. Thus, at total pressures greater than 10 torr (4% ketene in argon), we find $T_v \sim 2200$ K ($I_{CGF}/I_0 \sim 0.4$). This is in qualitative accord with the CO laser absorption results on this system reported by Lin and co-workers[8,16] and suggests that the T_v observed here corresponds to a nearly unrelaxed vibrational distribution. At ketene pressures of 0.04 torr, in the absence of argon, significantly less attenuation is observed with a CGF containing up to 500 torr of CO: $I_{CGF}/I_0 \gtrsim 0.6$. Since this fluorescence is viewed through a band-pass filter centered at 4.7 μm, it is not likely due to species other than CO. A CGF functions by selectively quenching emission from transitions that terminate on rovibrational states that are thermally populated. Thus, we conclude that at low pressures, a significant component of the CO fluorescence originates from high *rotational* states, i.e., rotational states not appreciably populated at 300 K. The extent to which CO emission associated with a specified rovibrational distribution would be attenuated by a CO CGF can be numerically simulated.[17] Thus, a CO rotational temperature, T_r, can be qualitatively estimated from our experimental I_{CGF}/I_0 at low pressures by assuming a Boltzmann distribution of rotational states. We find $T_r \sim 7000$ K, which is a *lower* limit since the nascent rotational distribution may relax to some extent during the rise time of our detection system. A non-Boltzmann rotational distribution could, however, give rise to the observed CGF behavior, and the average rotational energy might then be lower than that suggested by our T_r value.

Our data provide compelling evidence for the importance of rotational energy release in the photofragmentation of ketene at 193 nm. This has some relevance in the analysis of models for the potential surface associated with this reaction. Fluorescence has never been observed from excited ketene. Constraints imposed by electronic symmetry conservation indicate that only the ground state of ketene correlates with $CH_2(^1A_1)$ product. These points suggest that regardless of the reactant state populated at 193 nm, internal conversion to the ground state occurs prior to fragmentation. Ab initio surfaces for the dissociation of ketene suggest that both linear (eq 1) and/or nonlinear (eq 2) fragmentation



(1)

(2)

channels may be feasible.[12,13] These paths should be differentiable since, in (1), motion along the "reaction coordinate" correlates with product relative translation while in (2), this motion correlates with rotational excitation in the products. Thus (2) provides a means for efficiently coupling available energy into CO rotational degrees of freedom that is not available in the case of a linear decay mechanism, (1).

In conclusion, infrared fluorescence methods can provide useful information on rovibrational energy disposal in photofragmentation reactions. The photodissociation of ketene at 193 nm yields CO with a vibrational temperature of ca. 2200 K and a rotational temperature of $\gtrsim$7000 K. This result indicates that fragmentation occurs predominantly via a nonlinear channel (2).

(15) McNair, R. E.; Fulghum, S. F.; Flynn, G. W.; Feld, M. S.; Feldman, B. J. *Chem. Phys. Lett.* **1977**, *48*, 241–244.

(16) Lin and co-workers[8] define T_v by excluding all states with $v \geq 5$, but when the definition used in ref 15 is employed, their data yield $T_v \sim 2770$ K.

(17) Essentially, we calculate the emission spectrum of CO for a specified T_v and T_r and then the extent to which this emission is attenuated by a CGF containing CO at $T_v = T_r = 300$ K. Rosenfeld, R. N.; Sonobe, B. I., to be submitted for publication.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work. The excimer laser used here was obtained with funds provided by an NSF major instrumentation grant (CHE81-14966).

Registry No. Ketene, 463-51-4; carbon monoxide, 630-08-0.

Total Synthesis of the Major Human Urinary Metabolite of Prostaglandin D_2, a Key Diagnostic Indicator

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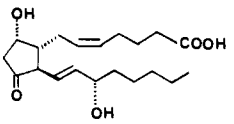
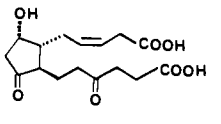
Systemic mastocytosis is a potentially fatal disease in which tissue mast cells proliferate excessively and produce abnormally large amounts of histamine and/or prostaglandin D_2 (**1**).[1] Di-



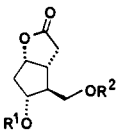
1



2

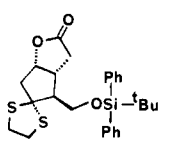
agnosis and proper treatment of this and other human illnesses in which PGD_2 is overproduced could in principle be facilitated by a urinary immunoassay for the major metabolite of PGD_2, the diketo acid **2**.[2] Surprisingly this key substance, which is not available in significant amount from any natural source, has not previously been synthesized. We report herein a practical synthetic route to **2** that also introduces several new and potentially valuable methods.

The readily available methoxy acetate **3**[3] was converted to the



3, R^1 = Ac, R^2 = CH_3

4, R^1 = H, R^2 = TBDPS



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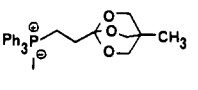

6

silyloxy alcohol **4** in 95% overall yield by the following sequence: (1) demethylation by exposure to 2 equiv of trimethylchlorosilane and 2 equiv of sodium iodide in dry acetonitrile at 50 °C for 4 h and subsequent extractive isolation;[4,5] (2) silylation by reaction with 1.5 equiv of *tert*-butyldiphenylsilyl (TBDPS) chloride and 2 equiv of 4-(dimethylamino)pyridine in methylene chloride at 0 °C for 30 min; (3) deacetylation with 1 equiv of potassium carbonate in dry methanol at 23 °C for 1.5 h followed by extractive isolation and stirring of the product with a catalytic amount of tosic acid in methylene chloride to cyclize a small amount of byproduct formed by lactone saponification. Oxidation of the

(1) Roberts, L. J., II; Sweetman, B. J.; Lewis, R. A.; Austen, K. F.; Oates, J. A. *New England J. Med.* **1980**, *303*, 1400.

(2) Ellis, C. K.; Smigel, M. D.; Oates, J. A.; Oelz, O.; Sweetman, B. J. *J. Biol. Chem.* **1979**, *254*, 4152.

(3) (a) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675. (b) Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, U.; Weinshenker, N. M. *Ibid.* **1970**, *92*, 397.

(4) Reactions involving air-sensitive reagents or substances were conducted under an inert atmosphere. Satisfactory spectroscopic data (infrared, proton magnetic resonance, and mass spectral) were obtained for each synthetic intermediate by using chromatographically purified and homogeneous samples.

(5) This procedure represents a major improvement over existing processes,[3] which is especially welcome because of its value in industrial PG synthesis.

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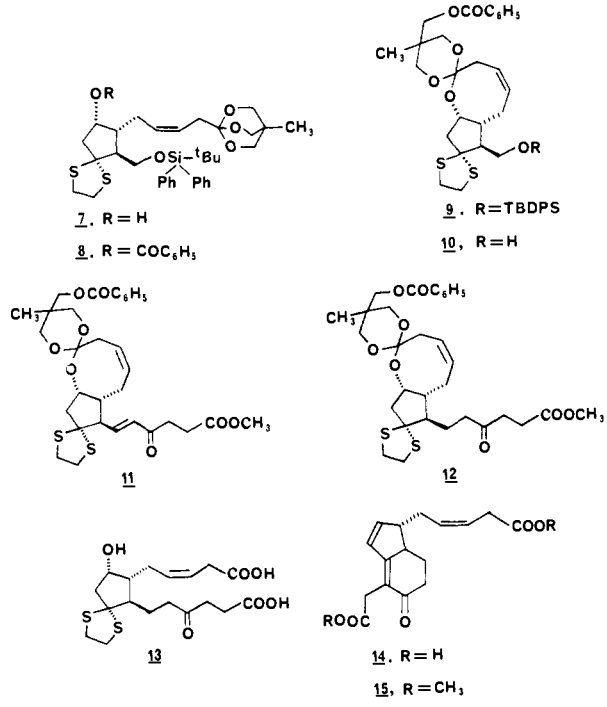
Chart I



alcohol **4** to the corresponding ketone was effected by reaction with 2 equiv of diisopropylcarbodiimide and 0.5 equiv of dichloroacetic acid in 1:1 benzene–dimethyl sulfoxide at 23 °C for 30 min (yield >90%). The conversion of this unstable, acid- and base-sensitive ketone to the corresponding ethylene thioketal with ethane-1,2-dithiol could not be accomplished by published procedures,[6] and a new method had to be developed. The use of anhydrous zinc triflate as catalyst was found to be extremely effective in this and a wide variety of other cases. Reaction of the crude keto lactone from **4** with 2 equiv of ethane-1,2-dithiol and 1.2 equiv of zinc triflate in methylene chloride at 23 °C for 5 h produced the desired thioketal **5** in 85% overall yield from **4**.[7]

The next phase of the synthesis, attachment of the necessary ring appendages, required novel protection techniques. Reduction of the lactone **5** with 1.0 equiv of diisobutylaluminum hydride in toluene at −78 °C for 30 min furnished quantitatively the corresponding lactol which was treated with the ylide from reaction of phosphonium iodide **6** and dimsyl sodium[8] in dimethyl sulfoxide at 25 °C for 4 h to give the (*Z*)-β,γ-unsaturated ortho ester–thioketal **7** in 90% yield.[9,10] Although the hydroxyl group in **7** could be protected readily by benzoylation using 4-(dimethylamino)pyridine–triethylamine and benzoyl chloride in methylene chloride at 23 °C which gave **8** in good yield, it was found that this intermediate was not suitable for the synthesis because of interference by the *Z* double bond in a subsequent step. Protection of the secondary hydroxyl function and the *Z* double bond could be achieved simultaneously simply by reaction of **7** with 3 equiv of benzoyl chloride and pyridine (6 equiv) in methylene chloride at 23 °C for 4 h to give the internal ortho ester **9** in 75% yield. Clearly pyridinium chloride is sufficiently acidic to catalyze isomerization of **7** to an eight-membered cyclic ortho ester–primary alcohol, which is benzoylated to form **9**. Desilylation of **9** (4 equiv of tetra-*n*-butylammonium fluoride in tetrahydrofuran (THF) at 50 °C for 9 h) afforded quantitatively the primary alcohol **10**, which by oxidation with 2 equiv of diisopropylcarbodiimide and 0.5 equiv of dichloroacetic acid in 1:1 benzene–dimethyl sulfoxide at 23 °C for 30 min was transformed into the corresponding aldehyde in >95% yield. Reaction of this aldehyde with the sodium salt of dimethyl 4-(methoxycarbonyl)-2-(oxobutyl)-phosphonate[11] in THF (made by using NaH–THF) at 23 °C for 2 h produced the enone **11** in 75% yield. Attempted reduction of the carbonyl-conjugated double bond of **11** with a variety of borohydride, hydride, and silane reagents[12] was unsuccessful. Therefore, a new method for the selective reduction of an α,β-enone to a nonconjugated ketone was sought that could be used with a substrate containing a thioketal unit and another nonconjugated double bond.

A highly satisfactory two-step process for the selective reduction of enone **11** was developed. Reaction of **11** with excess hydrogen sulfide and 1 equiv of potassium carbonate in dimethyl sulfoxide at 23 °C for 1 h resulted in 1,4-addition of H_2S to the α,β-enone to form the β-mercapto ketone, which upon isolation and treatment with excess tri-*n*-butylphosphine in benzene at 23 °C for 7 h with external irradiation (UV sunlamp) was desulfurized[13] to give **12** as desired in 65% overall yield.[14] This method, because of its mildness and tolerance of functionality, should find broad application in synthesis.

Exposure of **12** to 0.3 equiv of sulfuric acid in methanol at 23 °C for 5 min followed by treatment with 1 N sodium hydroxide in aqueous methanol at 23 °C for 10 h produced the thioketal diacid **13** (89%), which upon deketalization with 4 equiv of mercuric chloride and 4 equiv of calcium carbonate in 4:1 acetonitrile–water at 23 °C for 8 h afforded the PGD_2 metabolite **2** in 75% yield. Previously **2** has been obtained from urine in only submicrogram amount and identified by mass spectrometry.[2] The mass spectrum of the dimethyl ester bis(methoxyoxime)trimethylsilyl ether derivative of synthetic **2** was identical with that reported[2] for this derivative of the major PGD_2 urinary metabolite. The structure of synthetic **2** is clear from (1) the method of synthesis, (2) 270-MHz ^1H NMR spectra of **2** and **2** dimethyl ester, (3) mass spectrum of **2** dimethyl ester, (4) conversion by treatment with 0.32 M potassium hydroxide in 10:1 methanol–water at 50 °C for 16 h into the diacid **14**, UV_{max} (CH_3OH) 287 nm, and (5) esterification of **14** to the corresponding dimethyl ester **15** (using diazomethane), UV_{max} (CH_3OH) 288.5 (ϵ 20000), which was characterized by 270-MHz ^1H NMR and mass spectra.

The readily available synthetic PGD_2 metabolite **2** has been coupled to bovine serum albumin after carboxyl activation (1 equiv of isobutyl chloroformate and 1 equiv of triethylamine at 0 °C) to give an immunogen, which was then utilized to generate rabbit antibodies. Details of this work and on the development of an immunoassay for **2** will be reported separately.

(6) Among the procedures tried were those involving various protic acids, boron trifluoride etherate, zinc halides, or magnesium sulfate as catalysts. Also unsuccessful was the method of Evans [Evans, D. A.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L., *J. Am. Chem. Soc.* **1977**, *99*, 5009]. Starting material was either recovered unchanged or totally decomposed (probably as a result of initial β-elimination of the lactone oxygen) in numerous experiments.

(7) Further details and examples of this method appear elsewhere: Corey, E. J.; Shimoji, K. *Tetrahedron Lett.* **1983**, *24*, 169.

(8) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

(9) The trimethylthio ortho ester corresponding to **7** could also be prepared. However, we were unable to find conditions for the clean conversion of the thio ortho ester unit to carboxylic or carboxylic methyl ester functions without ethylene thioketal cleavage.

(10) The phosphonium iodide **6** was synthesized from 3-chloropropionitrile by the following sequence: (1) reaction with dry hydrogen chloride in 1:1 methanol–ether at 0 °C for 24 h to form the imido methyl ester hydrochloride; (2) reaction with 2-methyl-2-(hydroxymethyl)propane-1,3-diol in tetrahydrofuran at 40 °C for 3 h to form the cyclic ortho ester; (3) displacement of chloride by iodide using sodium iodide in dimethylformamide at 100 °C for 3 h; (4) reaction with triphenylphosphine in acetonitrile at reflux for 24 h in the presence of potassium carbonate.

(11) Dimethyl 4-(methoxycarbonyl)-2-(oxobutyl)phosphonate was synthesized in 82% yield by treatment of dimethyl methylphosphonate with 1 equiv of *n*-butyllithium in THF at −78 °C for 45 min to form the lithio derivative and subsequent reaction with dimethyl succinate (−78 °C for 1 h and 23 °C for 1.5 h).

(12) See, for example: (a) Ganem, B. *J. Org. Chem.* **1975**, *40*, 146. (b) Ojima, I.; Nihonyanagi, M.; Kogure, T.; Kumagai, M.; Horiuchi, S.; Nakatsugawa, K. *J. Organomet. Chem.* **1975**, *94*, 449.

(13) Hoffman, F. W.; Ess, R. J.; Simmons, T. C.; Hanzel, R. S. *J. Am. Chem. Soc.* **1956**, *78*, 6414.

(14) When this desulfurization process was applied to the β-mercapto ketone derived analogously from the benzoate ortho ester **8**, none of the desired product could be obtained due to the intramolecular addition of the intermediate carbon radical (β to carbonyl) to the *Z* double bond of the ortho ester side chain.

The synthetic approach described herein, which provides a practical route to **2**, also appears well suited to the synthesis of key metabolites of thromboxane A_2, with the inclusion of a Baeyer–Villiger oxidation in the multistep process.[15,16]

Supplementary Material Available: Listing of IR, NMR, and mass spectral data for the intermediates in this synthesis (7 pages). Ordering information is given on any current masthead page.

(15) We are indebted to Dr. Robert A. Lewis of the Harvard Medical School for drawing our attention to this problem and for collaboration on the immunoassay study.
(16) This work was supported in part by grants from the National Institutes of Health and the National Science Foundation.

Synthetic Applications of Titanocene Methylene Complexes: Selective Formation of Ketone Enolates and Their Reactions

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Contribution No. 6764 from the Laboratories of Chemistry California Institute of Technology Pasadena, California 91125

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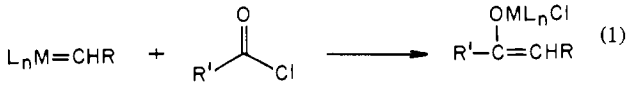
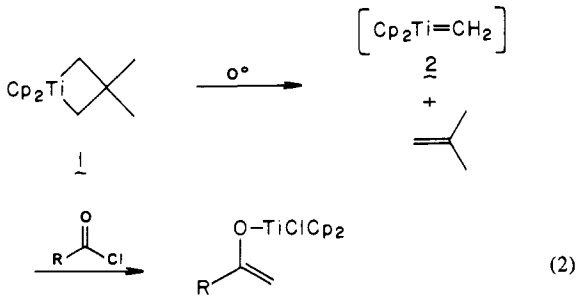
Over the past few years, the development of organo–transition-metal chemistry has provided new methods to solve classic problems in organic synthesis. One important development has been the use of group 4 enolates to control aldol stereochemistry;[1] however, their use is limited by the inability in many cases to form the enolate desired selectively. We report here a solution of the problem of regioselective enolate formation.

Early-transition-metal alkylidene complexes react with acid chlorides[2] to yield the corresponding enolate complex (eq 1). The



(1)

enolate is formed instead of the vinyl chloride expected as the product of Wittig-type chemistry.[3] The easily generated titanocene methylidene complex (**2**, eq 2) gives an excellent entry



(2)

into the most useful enolates, those of methyl ketones, which we have found to be of utility in synthetic reactions. This regiospecific synthesis of stable enolates avoids many of the problems of standard approaches.[4]

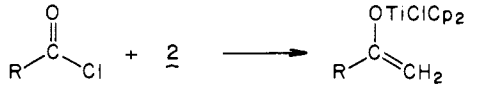
(1) (a) Evans, D. A.; McGee, L. R. *Tetrahedron Lett.* **1980**, *21*, 3975. (b) Yamamoto, Y.; Maruyama, K. *Ibid.* **1980**, *21*, 4607.
(2) Schrock, R. R.; Fellman, J. D. *J. Am. Chem. Soc.* **1978**, *100*, 3359.
(3) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1977**, *100*, 3611. (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *Ibid.* **1980**, *102*, 3270.
(4) (a) Stork, G.; Kraus, G. A.; Garcia, G. A. *J. Org. Chem.* **1974**, *39*, 3459. (b) Gaudemar-Bardone, F.; Gaudemar, M. *J. Organomet. Chem.* **1976**, *104*, 281. (c) Kuwajima, I.; Inoue, T.; Sato, T. *Tetrahedron Lett.* **1978**, 4887. (d) Mukaiyama, T.; Inoue, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174.

Table I.

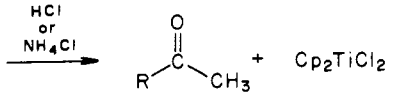
RC(O)Cl	reaction conditions[a] 0 °C	3 °C	15 °C	20 °C	RC(O)CH$_3$ yield, %[b]
benzoyl chloride	2		5		92[c]
pivaloyl chloride	5			75	96[c]
ethyl chloroformate	5			15	48[c]
ethylsuccinyl chloride	5	6			89[c]
phenylacetyl chloride	5	45			97[c]
3-phenylpropionyl chloride	5	45			87[d]
1-naphthoyl chloride	3		5		92[d]
5	10	45			76[e]

[a] The numbers reported for each acid chloride are the times, in minutes, that the reaction was allowed to stir first at 0 °C and then at a second, higher temperature. [b] Based on the amount of acid chloride added.[9] [c] Yield was determined by quantitative VPC analysis. Product was characterized by VPC and ^{1}H NMR comparison with an authentic sample. [d] Yield of isolated product from 1 mmol of acid chloride. Product was characterized by ^{1}H and ^{13}C NMR comparison with an authentic sample. [e] Yield of isolated product from 1 mmol of acid chloride. The reaction was quenched with saturated aqueous NH_4Cl. Product was characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy in addition to comparison with an independently synthesized sample. The product produced satisfactory C,H analysis.

The titanium methylidene complex is generated in situ from its aluminum dimethyl chloride,[3] olefin, acetylene, or phosphine adducts. For the applications below, the labile titanocyclobutane **1**, prepared from isobutylene is the most useful.[5] This reaction (eq 2) produces the enolates suitable for isolation with >95% conversion of **1** in the presence of a 50% excess of acid chloride. Other methylene sources such as the Tebbe reagent/pyridine[6] or adducts which require elevated temperatures[5] for the generation of **2**, result in substantially lower yields. Stable enolates can be isolated and characterized by spectroscopic and chemical methods (eq 3).[7]

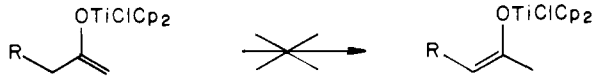


R = $(CH_3)_3C$–, p-Cl–C_6H_4–, CH_3CH_2–, $C_6H_5CH_2$–



(3)

Of particular importance is the lack of isomerization of **3** and **4** to their more stable isomers (eq 4). The regiostability of these



(4)

R = CH_3– (**3**), C_6H_5– (**4**)

complexes is further demonstrated by the conversion of an optically active acid chloride to the corresponding methyl ketone with ≤0.5% epimerization (eq 5).[8]

(5) Grubbs, R. H.; Straus, D. A. *Organometallics* **1982**, *1*, 1658. This complex and related metallacycles are easily prepared from commercially available $Cp_2TiCH_2AlMe_2Cl$.
(6) Use of the Tebbe reagent ($Cp_2TiCH_2AlMe_2Cl$) results in substantially lower yields (20%), since the aluminum byproducts induce decomposition of the enolate.
(7) All four isolated enolates are in complete agreement with the spectroscopic data. Representative spectroscopic data, that of **4** are as follows: ^{1}H NMR (CD_2Cl_2, −30 °C) δ 3.27 (s, 2 H), 3.85 (s, 1 H), 3.96 (s, 1 H), 6.20 (s, 10 H), 7.31 (m, 5 H); ^{13}C NMR (CD_2Cl_2, −30 °C) δ 43.4 (CH_2), 87.4 (=CH_2), 117.2 (Cp), 126.3 (Ph), 128.3 (Ph), 129.4 (Ph), 139.0 (Ph), 173.2 (=C—O).

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