Reactions of "$Cp_2Ti{=}CH_2$"† Sources with Acid Anhydrides and Imides‡

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The reaction of $Cp_2\overline{TiCH_2C(Me)_2CH_2}$ (**3a**) with acid anhydrides gave $Cp_2Ti(OC(O)R)(OC(R){=}CH_2)$ (**4**) in moderate yields. Reaction of **4** with **3a** and anhydrides produced $[Cp_2Ti(OC(R){=}CH_2)]_2O$ (**5**) and $Cp_2Ti(OC(O)R)_2$ (**7**), respectively. The enolate **4c** (R = Ph) reacted with benzaldehyde to form the dehydrated aldol product chalcone (**8**). Selected 2,5-pyrrolidinediones upon treatment with 1 equiv of $Cp_2TiCH_2{\cdot}AlMe_2Cl$ (**1**) or **3a** yielded mixtures of 5-methylene-2-pyrrolidinones and 2,5-dimethylenepyrrolidines while use of 2 equiv of **1** or **3a** gave exclusively the dimethylene products, potential "dienamine" precursors of 1,2,5-trisubstituted pyrroles. Regioselective methylene transfer was observed for 3,3-dimethyl-2,5-pyrrolidinediones, giving 3,3-dimethyl-5-methylene-2-pyrrolidinones in high yields. Treatment of 1-(3-butenyl)-3,3-dimethyl-5-methylene-2-pyrrolidinone (**12n**) (formed from the parent 2,5-pyrrolidinedione and **1**) with HCO_2H gave the cyclized product 1-aza-4-(formyloxy)-6,8,8-trimethylbicyclo[4.3.0]nonan-9-one (**14a**) exemplifying a potential method for the synthesis of alkaloid analogues. Reaction of 3,3-dimethyl-2,6-piperidinediones with either **1** or **3a** formed mixtures of the single methylene-transfer products 3,3-dimethyl-5-methylene-2-piperidinones and titanium enolates of the starting 2,6-piperidinediones. The enolate (**16d**) of 3,3-dimethyl-1-(2,6-dimethylphenyl)-2,6-piperidinedione was unreactive toward benzaldehyde, even upon prolonged heating.

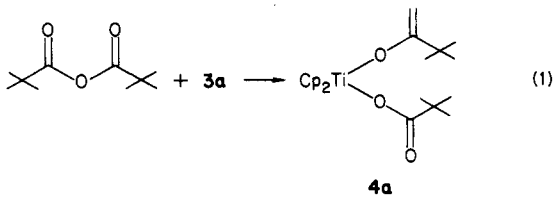
In 1978 Tebbe and co-workers reported[1] the isolation of the titanium alkylidene **1** and the subsequent reactions with several substrates, including the conversion of cyclohexanone into methylenecyclohexane. Further studies by other investigators[2] have developed a variety of useful synthetic transformations of carbonyl substrates with this reagent and titanacyclobutanes, both of which serve as sources of the highly reactive titanocene methylidene **2** (Scheme I).

Principally, three pathways of reactivity of **2** with carbonyl compounds are known (Scheme II). The different reactivity patterns may be explained by the following sequence of steps. Initial coordination of the carbonyl oxygen to the titanium in **2** gives a Lewis acid–base complex. This is followed by formation of an oxymetallacycle intermediate except for hindered ketones where the lower energy pathway appears to be deprotonation of the ketone to yield the titanium enolate of the original ketone[3] (path A). Decomposition of the oxymetallacycle produces $(Cp_2Ti{=}O)_n$ and the methylene-transfer product for unhindered ketones,[3] aldehydes,[4] esters,[5] and amides [6] (path B). Alternatively, the intermediate derived from **2** and acid chlorides rearranges to give an enolate,[7] presumably due to the lability of the chloride substituent as compared to those of the other complexes.

In this report the reaction of **2** with acid anhydrides and imides, which show examples of all three pathways, is discussed. These examples show all three reaction paths in selected systems and demonstrate the subtle features that control the relative rates of each pathway.

Results and Discussion

Reaction of 2 with Acid Anhydrides. Pivalic anhydride (trimethylacetic anhydride) upon treatment with **3a** gave the enolate **4a** (eq 1). Apparently the carboxylate

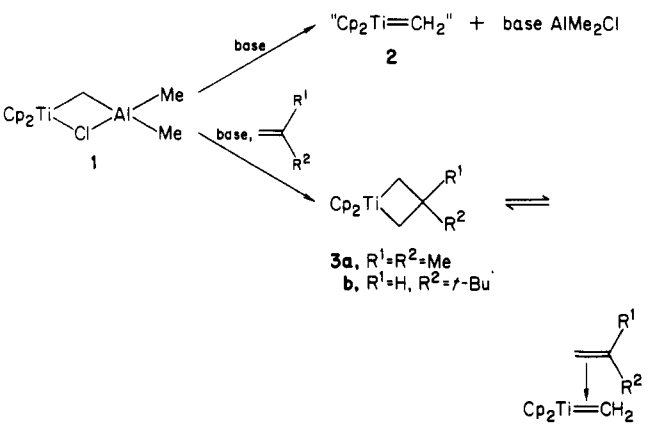


(1)

4a

substituent of the oxymetallacycle intermediate is comparable in lability to the chloride as none of the product resulting from methylenation was observed. An NMR tube reaction in C_6D_6 with 1.2 equiv of anhydride led to a 70% yield of enolate which was stable over several hours at room temperature to excess anhydride still present (^1H NMR). Isolation of **4a** was achieved in 55% yield with a 1:1 ratio of reactants in pentane. Recrystallization from pentane afforded crystals of **4a** that were unsuitable for structure analysis as were crystals isolated from toluene/pentane, ether, and THF/hexane. Upon very slow cooling of the solutions over many days (to obtain crystals for structure determination) significant decomposition of the enolate occurred and the crystals obtained were of much lower purity with the impurities present being $Cp_2Ti(OC(O)$-t-$Bu)_2$ (**7a**)[8] and the methyl ketone pinacolone (^1H NMR).

Scheme I



† Cp = cyclopentadienyl.

‡ Contribution No. 7134.

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(2) For a review on these studies, see: Brown-Wensley, K. A.; Buchwald, S. L.; Cannizzo, L. F.; Clawson, L. E.; Ho, S.; Meinhart, J. D.; Stille, J. R.; Straus, D.; Grubbs, R. H. *Pure Appl. Chem.* **1983**, *55*, 1733.

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(4) Brown-Wensley, K. A. Ph.D. Thesis, California Institute of Technology, Pasadena, 1981.

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(6) Pine, S. H., private communication.

(7) Stille, J. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1983**, *105*, 1664.

(8) Identified by comparison (^1H, ^{13}C NMR, IR) to independently synthesized sample (see Experimental Section).

(9) Obtained from D. A. Straus.

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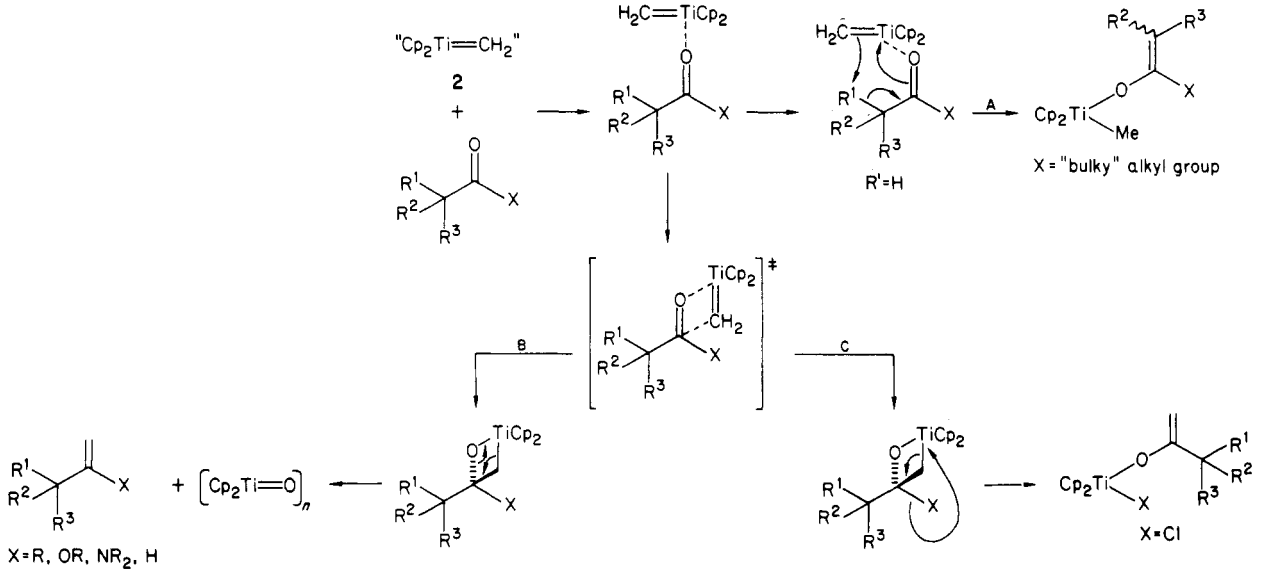
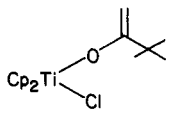
Scheme II



Compound **4a** did not react with pivaldehyde at room temperature nor at higher temperatures at which the enolate decomposed. In contrast, the analogous reaction employing the enolate **11** leads to a 67% yield of the aldol product.[7]



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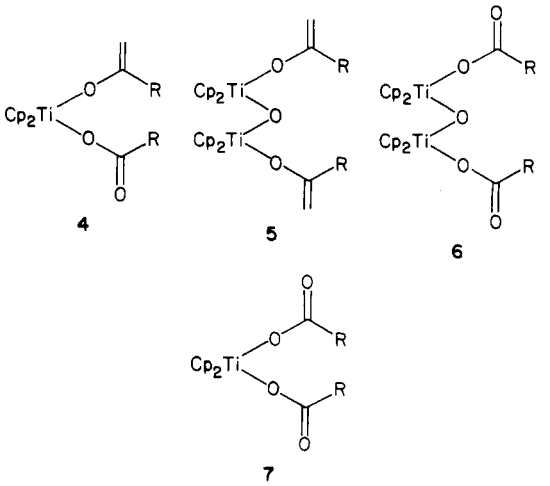
Upon treatment with **3a** in C_6D_6, acetic anhydride was transformed into the enolate **4b** (^1H NMR). Acidolysis with anhydrous HCl precipitated Cp_2TiCl_2 and gave acetone and acetic acid in the supernatant (identified by ^1H NMR and GC analysis). Reaction of the initially formed enolate with starting materials present in solution was also observed, yielding additional products (vide infra). Similar results were also obtained with propionic and butyric anhydrides.

A series of NMR tube experiments were conducted to study the subsequent reactions of the enolate **4b**. It was



4 **5** **6** **7**

a, R = *t*-Bu; **b**, R = Me; **c**, R = Ph

found that the yield of **4b** (based on limiting reagent) varied dramatically depending upon the ratio of anhydride to **3a** employed (Table I). The highest yield of **4b** was obtained with a 1:1 ratio of reactants although substantial amounts of side products were still present. The presence of excess **3a** gave a lower yield of **4b** and an increase in formation of $(Cp_2Ti(OC(Me){=}CH_2))_2O$ (**5b**). In contrast, a lower yield of **4b** and an increase in formation of $(Cp_2Ti(OC(O)Me))_2O$ (**6b**) and $Cp_2Ti(OC(O)Me)_2$ (**7b**) was observed when excess anhydride was employed. Attempted isolation of **4b** using a 1:1 ratio of reactants was unsuccessful with a variety of solvents, temperatures, and reaction times. In one trial with ether as a solvent and a reaction time of 80 min at 0–5 °C, an impure sample of **6b** was isolated in an 11% yield from the reaction mixture. NMR analysis of the supernatant indicated a complex mixture of **4b**, **5b**, **7b**, and other compounds present. Compound **6b** was identified by ^1H and ^{13}C NMR, IR and acidolysis with anhydrous HCl to give acetic acid and Cp_2TiCl_2. It underwent slow conversion to **7b** and $(Cp_2Ti{=}O)_n$ upon standing at room temperature in C_6D_6 or $CDCl_3$.

Table I. Products from 3a and $(MeCO)_2O$

ratio of reactants 3a/$(MeCO)_2O$	% yield based on limiting reagent[a]			
	4b[b]	5b[b]	6b[c]	7b[c]
0.10	*d*	*d*	*d*	*d*
0.5	25	0	5	20
0.8	43	17	20	11
0.9	46	18	16	16
1.0	47	37	13	6
1.1	40	40	15	4
1.4	19	54	20	10
1.9	*d*	50	20	*d*
2.2	*e*	*e*	*e*	*e*

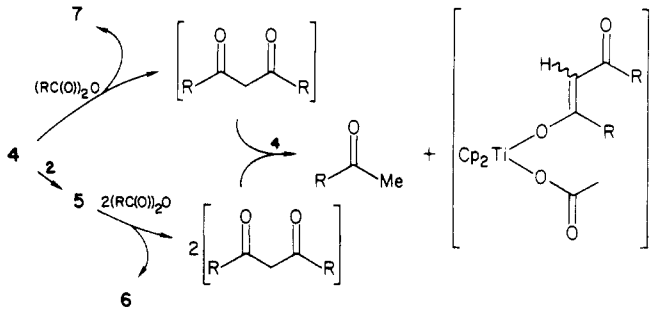
[a] Percent yields based on NMR peak heights (±5%). [b] Identified by comparison of ^1H NMR to similar compounds. [c] Identified by ^1H NMR comparison to authentic samples (**6b**,[8] **7b**[9]). [d] Not observable by NMR (<5%). [e] Spectrum uninterpretable.

The reaction between **3a** and benzoic anhydride produced the enolate **4c** (R = Ph), but further reaction of the enolate was again observed. The product was obtained in 40–60% crude yield after workup. NMR analysis of a typical sample collected gave approximately 60% **4c**, 10% **5c**,[8] 10% **6c**,[10] and 10% **7c**.[11] Reaction of **4c** with benzaldehyde was slow at room temperature (several hours) and was accompanied by decomposition of the enolate. At 50

(10) Identified by comparison of ^1H NMR to **6b**.

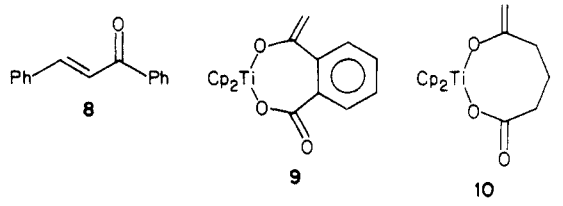
(11) For a recent synthesis of **7c**, see: Hoffman, D. N.; Chester, N. D.; Fay, R. C. *Organometallics* **1983**, *2*, 48.

Scheme III. Subsequent Reactions of 4



°C the reaction proceeded quickly (15 min) with less decomposition of the enolate (^{1}H NMR). Workup of the mixture afforded the dehydrated aldol product chalcone (**8**) in an unoptimized 27% yield.

Upon reaction with **3a** (NMR tube reaction), phthalic anhydride yielded a ^{1}H NMR consistent with formation of the proposed enolate **9** (46% yield), while similar



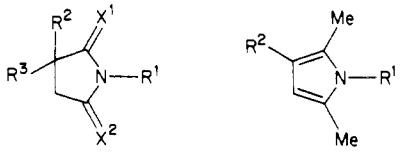
treatment of glutaric anhydride indicated formation of the proposed enolate **10** (44% yield). Maleic and succinic anhydrides upon treatment with **3a** gave only insoluble polymeric material and no observable enolate by ^{1}H NMR.

As previously mentioned the enolates formed from acid anhydrides and **3a** undergo further reactions once formed in solution. An overall mechanism consistent with the products observed is presented in Scheme III. The further reactions of **4** are proposed to occur as follows. Acylation of the enolate by excess anhydride affords the corresponding β-diketone with concomitant formation of the titanocenedicarboxylate **7**. The acidic β-diketone protonates another molecule of enolate to give the methyl ketone and a titanocenecarboxylate–β-diketonate complex. Additionally, **4** can react with **2** present, yielding the μ-oxo-complex **5**. This complex behaves similarly to **4**, giving the new μ-oxo complex **6** and 2 mol of β-diketone, upon reaction with anhydride.

Reaction of 2 with Imides. Imides, analogous in structure to acid anhydrides, were expected to undergo methylenation upon reaction with **2** due to the poor leaving group ability of –NC(O)R compared to –OC(O)R (Scheme II). Wittig reagents are known to react with imides to give alkenylation products in low yields.[12] The reaction appears to be limited by steric hindrance with low yields reported for succinimides (2,5-pyrrolidinediones) and in only exceptional cases could glutarimides (2,6-piperidinediones) be alkenylated.

A. Succinimides. Treatment of 1-phenyl-2,5-pyrrolidinedione (**12a**) (Chart I) with 1 equiv of **3a** yielded a 1:1:1 mixture of starting material and the methylene-transfer products **12b,c** (^{1}H NMR). Employing 2 equiv of **3a** led to quantitative formation (^{1}H NMR) of **12c**, which rapidly isomerized upon contact with moisture in the air to the pyrrole **13a**.[13] In reacting 1.9 equiv of **12a**

Chart I



	R^1	R^2	R^3	X^1	X^2		R^1	R^2
12a	Ph	H	H	O	O	**13a**	Ph	H
b	Ph	H	H	CH_2	O	**b**	Me	H
c	Ph	H	H	CH_2	CH_2	**c**	Ph	Me
d	Me	H	H	O	O			
e	Me	H	H	CH_2	O			
f	Me	H	H	CH_2	CH_2			
g	Ph	Me	H	O	O			
h	Ph	Me	H	O	CH_2			
i	Ph	Me	H	CH_2	CH_2			
j	Ph	Me	Me	O	O			
k	Ph	Me	Me	O	CH_2			
l	Ph	Me	Me	CH_2	CH_2			
m	3-butenyl	Me	Me	O	O			
n	3-butenyl	Me	Me	O	CH_2			
o	2,6-dimethylphenyl	Me	Me	O	O			
p	2,6-dimethylphenyl	Me	Me	O	CH_2			

with **3a** a 69:31 ratio of **12b** to **12c** was observed (^{1}H NMR). Similar results were obtained utilizing **1** as a source of **2**. Additionally, 1-methyl-2,5-pyrrolidinedione (**12d**) gave in the same manner the methylene-transfer products **12e,f** and the pyrrole **13b**.[13] Apparently, the rates of methylene transfer from **2** to the pyrrolidinediones **12a,d** and the methylenepyrrolidinones **12b,e** are very similar under the conditions employed, giving the observed product ratios. Unfortunately, **3a** is not reactive at lower temperatures (<0 °C) where regioselectivity may be possible and use of **1** (–40 °C, THF) on a preparative scale necessitates a basic aqueous workup which would isomerize and/or decompose the products. The dimethylene compounds **12c,f** could serve as potential sources of 1,2,5-trisubstituted pyrroles upon alkylation or acylation.

A single methyl group adjacent to one of the imide carbonyls imparted partial regioselectivity as evidenced by a 60:20:20 ratio of the methylenepyrrolidinone **12h**, the dimethylenepyrrolidine **12i**, and the starting pyrrolidinedione **12g** upon treatment of **12g** with 1 equiv of **3a** (^{1}H NMR). Use of **1** at –40 °C was not successful as **12h,i** decomposed upon workup of the reaction mixture and only

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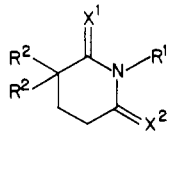
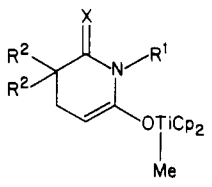
Chart II





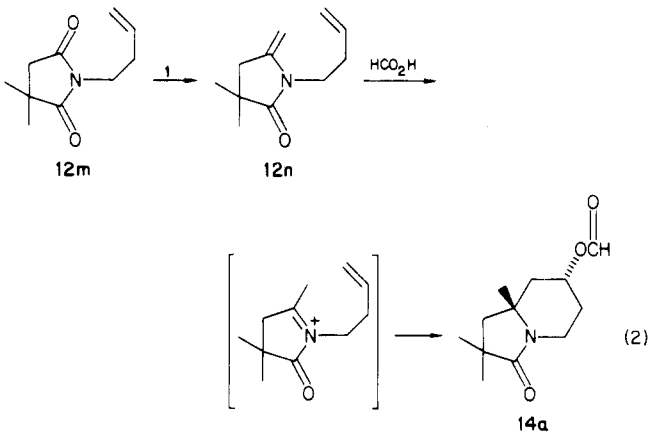
	R^1	R^2	X^1	X^2
15a	Ph	Me	O	O
b	Ph	Me	O	CH_2
c	Ph	H	O	O
d	Ph	H	O	CH_2
e	Ph	H	CH_2	CH_2
f	2,6-dimethylphenyl	Me	O	O
g	2,6-dimethylphenyl	H	O	O
h	CH_2Ph	Me	O	O
i	CH_2Ph	Me	O	CH_2
j	Me	Me	O	O
k	Me	Me	O	CH_2

	R^1	R^2	X
16a	Ph	Me	O
b	Ph	H	CH_2
c	Ph	H	O
d	2,6-dimethylphenyl	Me	O
e	2,6-dimethylphenyl	H	O
f	CH_2Ph	Me	O

the pyrrole **13c**[30] was isolated (8% yield).

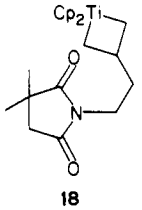
Introduction of two methyls into one of the α-positions of **12a**, to give **12j**, resulted in highly regioselective methylene transfer to the least hindered carbonyl. Employing **3a** produced a 96:4 ratio of **12k** to **12l** (^1H NMR) while use of **1** at −40 °C followed by basic aqueous workup gave in very high yield exclusively **12k**. Thus, quaternization of one of the α carbons leads to both high regioselectivity and increased stability of the methylene-transfer product.

Exploitation of this reactivity was accomplished by transformation of the pyrrolidinedione **12m** (synthesized by the procedure of Mitsunobu[29]) to the methylenepyrrolidinone **12n**. Subsequent treatment with HCO_2H[14] gave exclusively the cyclized product **14a** (69% isolated yield), presumably by trapping the intermediate α-acyl immonium ion (eq 2). In treating **12m** with **1**, the crude



(2)

product obtained after workup contained unreacted **12m**, even when excess **1** was employed. A NMR tube reaction with **3a** as a source of **2** yielded a mixture (3:1) of **12n** to the metallacycle **18**. This type of metallacycle[15] (with a



single β-substituent) is stable at room temperature and

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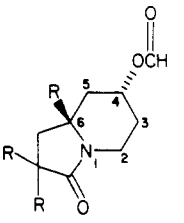
Table II. Selected Shifts (ppm) and Coupling Constants (Hz) from ^1H NMR Spectra[a] of 14a,b

	14a	14b
OCH	8.03 (s)	8.05 (s)
H_4	5.22 (t of t, J_1 = 12, J_2 = 11, $J_3 = J_4$ = 4.4 Hz)	5.05 (t of t, $J_1 = J_2$ = 11, $J_3 = J_4$ = 4 Hz)
H_2(e)	4.15 (m, J_1 = 14, J_2 = 5.4, J_3 = 2 Hz)	4.25 (m, J_1 = 14, J_2 = 5.5, J_3 = 2 Hz)
H_2(a)	2.86 (t of d, J_1 = 13, J_2 = 14, J_3 = 3 Hz)	2.76 (t of d, $J_1 = J_2$ = 14, J_3 = 3 Hz)

[a] Recorded in $CDCl_3$ (values for **14b** from ref 16a).

heating at 50 °C for 20 min was needed to complete decomposition. Unfortunately, the yield of **12n** did not increase after decomposition of **18** and **12m** was recovered after workup. Using **1** as the methylene source, the total isolated yield of **14a** was 51% based on **12m**.

Assignment of the stereochemistry of **14a** is based upon



14a, R=Me
b, R=H

comparison of its ^1H NMR spectrum to the related compound **14b** synthesized by Speckamp and co-workers[16a] (see Table II). The shift of the formate protons are nearly identical in both structures while the value of H_4, H_2-e, and H_2-a are very similar. More importantly, for both compounds the splitting patterns and coupling constants for these protons are the same. The assignment of trans stereochemistry (relative to the formate group) of the methyl group on C6 is based upon the presumed trans coplanar addition of the olefin to the α-acyl immonium ion.[16b] No other isomers of **14a** were observed by ^1H NMR in either the crude reaction mixture or the purified product. Speckamp and co-workers have made extensive use of the α-acyl immonium ion in a number of alkaloid syntheses[17] and use of the above sequence of reactions could potentially provide useful precursors to alkaloid analogues.

B. Glutarimides. Treatment of imide **15a** with 1 equiv of **1** at −40 °C in THF gave upon workup a quantitative yield of the original imide (Chart II). In an attempt to understand this result a NMR tube experiment utilizing

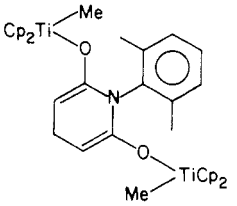
Table III. Reaction of 15j with "$Cp_2Ti{=}CH_2$" Sources[a]

run	% yield of 15k	temp, °C	solvent[a]	"$Cp_2Ti{=}CH_2$" source
1	54, 57[b]	−78	PhMe, pyr	1
2	59	−40	PhMe, pyr	1
3	60	−20	PhMe, pyr	1
4	62	20	PhMe, pyr	1
5	63, 65[b]	60	PhMe, pyr	1
6	55	−40	THF	1
7	52	−40	THF, pyr	1
8	56	−78	THF, PhMe	1
9	62	0	C_6D_6, pyr	1
10	72	20	C_6D_6	3a
11	71	58	C_6D_6	3b

[a] See Experimental Section for procedures. [b] Values of two different trials.

3a as a source of 2 was conducted. The ^1H NMR showed a 69:31 ratio of the enolate 16a to the methylene-transfer product 15b, indicating that treatment with 1 at −40 °C had given exclusively 16a (which was protonated upon workup) while the NMR tube reaction had followed both paths A and B, Scheme II. Similarly, treatment of the imide 15c with 3a resulted in a mixture of the starting imide 15c (20%), methylene-transfer products 15d (55%) and 15e (10%), the combined methylene-transfer and enolized product 16b (9%), and the enolate 16c (7%) while use of 2 equiv of 3a with 15c gave 15e (55%), 16b (40%), and 16c (5%) (^1H NMR).

The more sterically hindered glutarimides 15f and 15g were treated with 3a, giving exclusively the enolates 16d and 16e, respectively (in the reaction of 15g with 3a a small amount of the proposed dienolate 17 (5%) was also observed) (^1H NMR). Compound 16d was quite stable thermally and showed no decomposition or reaction with 3 equiv of benzaldehyde in C_6D_6 after 60 h at 60 °C. Synthesis of 16d (44% isolated yield) from 3a and 15f produced analytically pure crystals that were unfortunately unsuitable for X-ray structure analysis.



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The less sterically hindered glutarimide 15h upon reaction with 3a (NMR tube experiment) gave a 50:50 mixture of the methylene-transfer product 15i and the enolate 16f. Use of 1 (−40 °C, THF) and workup afforded a 42% yield of 15i after chromatography. In an attempt to optimize the yield of methylene-transfer product, the reaction of imide 15j with several sources of 2 under a variety of conditions was studied with the results summarized in Table III. Utilization of 1 gave lower yields of methylenation (runs 1–9) compared to 3a–b (runs 10 and 11). The trend toward higher yields of 15k with increasing temperature implies entropy favors methylenation over enolization in this system.

C. Enolization vs. Methylenation. As discussed above, the reaction of 2 with imides proceeds by two pathways. 2,5-Pyrrolidinediones undergo methylenation exclusively while 2,6-piperidinediones are predominantly enolized. However, methylenation does proceed to some degree when the substituent on nitrogen is less bulky. In an attempt to observe enolization of a 2,5-pyrrolidinedione by 2, the imide 12o (containing a very bulky nitrogen substituent) was allowed to react with 3a in an NMR tube experiment and gave exclusively the methylenation product 12p (none of the enolized product was observed). Treatment of 12o with 1 (−40 °C, THF) also gave only 12p. In contrast, the 2,6-piperidinedione analogue 15f yielded only the enolate 16d under the same experimental conditions (vide supra).

A possible explanation for the different reactivities of 12o and 15f toward 2 is as follows. Steric inhibition (by the 2,6-dimethylphenyl group on the nitrogen) toward formation of the oxymetallacycle intermediate needed for methylenation is essentially identical for both imides. Therefore the controlling factor in pathway determination appears to be the "availability" (for enolization) of the hydrogens on the carbon adjacent to the carbonyl. As expected, X-ray structures of several 2,5-pyrrolidinediones have shown the five-membered ring to be essentially planar with both α hydrogens in pseudoequatorial positions.[18] However, structures of 2,6-piperidinediones have shown one α proton to be axial and one to be equatorial for the six-membered, half-chair ring with very small torsional angles for the C4–C5–N–C1 and C5–N1–C1–C2 frameworks (the C3 carbon is out of the plane by ~0.6 Å).[19] Preferential enolization of the axial hydrogen α to the carbonyl in cyclohexanone is presumably due to stabilization of the developing filled p orbital of the enolized carbon with the p orbitals of the C–O framework.[20] From above, 2,6-piperidinediones contain an enolizable axial hydrogen while 2,5-pyrrolidinediones do not, and therefore one may conclude the observed enolization of the former is due to the favored (vide supra) axial hydrogen abstraction.

Another possibility is that the increased flexibility of the six-membered ring of 2,6-piperidinediones (compared to 2,5-pyrrolinediones) allows for proper orientation of the hydrogen for enolization to proceed. Further studies are needed to determine the geometrical requirements for enolization of 2,6-piperidinediones by 2.

Conclusion

In summation, the reaction of the titanocene methylidene 2 with anhydrides and imides proceed by the three known pathways (enolate formation, methylenation, and enolization) of carbonyl compound reactivity toward 2. Anhydrides are transformed into titanium enolates, presumably by migration of the carboxylate substituent of the oxymetallacycle intermediate. Succinimides (2,5-pyrrolidinediones) cleanly undergo methylenation at both carbonyl moieties with regioselectivity possible when one carbonyl is sterically hindered. Glutarimides (2,6-piperidinediones) are predominantly enolized by 2 (forming titanium enolates) with methylenation also observed as a competing reaction.

Experimental Section

General Procedures. All work involving air and/or moisture sensitive compounds was performed using standard high-vacuum or Schlenk line techniques under argon purified by passage through columns of BASF RS-11 (Chemalog) and Linde 4-Å molecular sieves and a Vacuum Atmospheres drybox under nitrogen. ^1H and ^{13}C NMR spectra were recorded on a Varian Associates EM-390 (90 MHz ^1H), XL-200 (200.15 MHz ^1H, 50.4 MHz ^{13}C) or a JEOL FX-90Q (89.60 MHz ^1H, 22.53 MHz ^{13}C). Chemical shifts are referenced to residual protiosolvent residues. IR spectra were recorded on a Beckman 4240. GC analysis was done using a Varian 1400 flame-ionization instrument equipped with a Spectra-Physics System I computing integrator and 10' 10% FFAP on 80/100 Chromosorb PAW column. Thin-layer chromatography (TLC) was performed on precoated TLC plates (silica gel 60 F-254, EM reagents). Flash chromatography was

performed by the procedure of Still et al.[21] using silica gel 60 (230–400 mesh ATM, EM Reagents). Melting points were recorded on a Thomas Hoover melting point apparatus and are uncorrected. Elemental analysis was performed by L. Henling at the analytical facility of the California Institute of Technology.

Materials. Tebbe's reagent ($Cp_2TiCH_2{\cdot}AlMe_2Cl$) (**1**),[22] $Cp_2\overline{TiCH_2C(CH_3)_2CH_2}$ (**3a**),[15] and $Cp_2\overline{TiCH_2CH(t\text{-}Bu)CH_2}$ (**3b**),[15] were synthesized according to established procedure. All acid anhydrides were purchased from Aldrich, except pivalic anhydride, and purified before use as follows: liquid anhydrides were fractionally distilled and stored under nitrogen; solid anhydrides were dissolved in an organic solvent, washed with 5% $NaHCO_3$ (aqueous) (3×) and H_2O (1X), dried (Na_2SO_4), evacuated to dryness, recrystallized, dried under high vacuum, and stored under nitrogen. Pivalic anhydride was made by the procedure of Ansell et al.[23] and stored under nitrogen. 1-Phenyl-2,5-pyrrolidinedione (**12a**) (Pfaltz & Bauer) and 1-methyl-2,5-pyrrolidinedione (**12d**) (Alfa Products) were recrystallized (EtOH) before use. 3-Methyl-1-phenyl-2,5-pyrrolidinedione (**12g**), 3,3-dimethyl-1-phenyl-2,5-pyrrolidinedione (**12j**), and 1,3,3-trimethyl-2,6-piperidinedione (**15j**) were made according to the procedure of Speckhamp et al.[24] 1-Phenyl-2,6-piperidinedione (**15c**) was synthesized by the procedure of Devlin et al.[25] $NaO_2CC(CH_3)_3$ was synthesized by treating the organic precursor with alcoholic NaOH, washing the collected salt liberally with Et_2O, and drying under high vacuum at 50 °C for 1 h. Benzaldehyde (Aldrich) was prepurified by the procedure of Perrin, Armarego, and Perrin.[26] Pivaldehyde (Aldrich) was dried over $MgSO_4$ before use. Cp_2TiCl_2 (Boulder) was purified by soxhlet extraction with CH_2Cl_2 before use. Toluene, benzene, THF, and diethyl ether were dried (CaH_2), transferred to sodium benzophenone ketyl, and later distilled into solvent flasks equipped with a Teflon screw-type valve. Pentane and hexane was stirred over concentrated H_2SO_4, washed with H_2O, dried over $MgSO_4$, transferred to sodium benzophenone ketyl in tetraglyme, and later distilled as above. Methylene chloride was dried over P_2O_5, degassed on the vacuum line for several minutes, and distilled as above. Benzene-d_6 (Merck, Sharp & Dohme) was transferred to sodium benzophenone ketyl, later distilled, and stored in the drybox.

General Procedures for NMR Tube Reactions. Reagents (if solids) were weighed and added to an NMR tube in the drybox and the tube was capped with a rubber septum. The tube was brought out and cooled to −20 °C in a dry ice–acetone bath. C_6D_6 was first added slowly from a gas-tight syringe so that it froze before mixing with the solid(s) present. Any liquid reagents were added on top of the C_6D_6 by syringe. The tube was thawed by hand warmth and shaken vigorously for several minutes and the spectrum recorded.

Synthesis of $(C_5H_5)_2Ti(OC(O)t\text{-}Bu)(OC(t\text{-}Bu){=}CH_2)$ (4a). To a Schlenk tube cooled to −10 °C and charged with **3a** (0.395 g, 1.59 mmol) was added 3 mL of −10 °C pentane via syringe. Pivalic anhydride (0.296 g, 1.59 mmol) was added via syringe and the mixture briefly stirred, warmed to 2 °C, and stirred for another 90 min. The solution was allowed to warm to room temperature and the dark supernatant transferred to another argon-filled Schlenk tube via cannula. The remaining orange solid was washed (1×, 1 mL, pentane), the washing added to the supernatant, and this combined mixture slowly cooled to −50 °C. The large orange-red crystals that deposited were collected, washed (2×, 0.5 mL, pentane, −50 °C), and dried under high vacuum to give 0.329 g of **4a** (55% yield, ^1H NMR integration with an internal standard gave >90% purity): ^1H NMR (C_6D_6) δ 6.06 (s, 10 H), 3.87 (s, 1 H), 3.26 (s, 1 H), 1.33 (s, 9 H), 1.13 (s, 9 H); ^{13}C NMR (C_6D_6) δ 182.7, 181.1, 116.2, 80.8, 40.2, 37.8, 28.5, 28.2. IR (C_6D_6) 2960, 1636, 1614, 1480 1391, 1307, 1290, 1206, 1182, 1034, 1016, 810 cm^{-1}. Anal. Calcd for $C_{21}H_{30}O_3Ti$: C, 66.66; H, 7.99. Found: C, 66.31; H, 7.72.

NMR Studies of the Reaction between 3a and Acetic Anhydride (results presented in Table I). Reactions were NMR tube experiments in which the concentrations of the reactants, reaction conditions, and times at which the spectra were recorded were duplicated as best as possible for each run. ^1H NMR (C_6D_6), **4b**, δ 6.05 (s, 10 H), 3.95 (s, 1 H), 3.78 (s, 1 H), 1.98 (s, 3 H), 1.71 (s, 3 H), **5b**, 6.03 (s, 20 H), 3.97 (s, 2 H), 3.78 (s, 2 H), 1.77 (s, 6 H), **6b**, see preparation of **6b** this section, **7b**,[9] 6.13 (s, 10 H), 1.94 (s, 6 H).

Synthesis of $(C_5H_5)_2Ti(OC(O)Ph)(OC(Ph){=}CH_2)$ (4c). To a Schlenk tube charged with **3a** (0.228 g, 0.919 mmol) and $(PhCO)_2O$ (0.209 g, 0.924 mmol) and cooled to −10 °C was added 2 mL of −10 °C Et_2O. The mixture was stirred and allowed to warm to 0 °C. An orange precipitate began to form after 20 min and stirring was continued another 25 min. The mixture was then recooled to −20 °C and the fine orange precipitate collected, washed (2×, 0.5 mL, Et_2O, −20 °C), and dried under high vacuum to give 0.154 g (40% yield) of impure product containing 60% **4c** (^1H NMR (C_6D_6) δ 8.49 (m, 2 H), 7.70 (m, 2 H), 7.20 (m, 6 H), 6.05 (s, 10 H), 4.77 (s, 1 H), 4.06 (s, 1 H); ^{13}C NMR (C_6D_6) δ 171.5, 170.1, 135.9, 131.4, 130.3, 127.0, 125.7, 117.1, 86.1; IR (C_6D_6) 3238, 1640, 1615, 1445, 1320, 810 cm^{-1}) along with 10% **5c** (see below), 10% **6c** (^1H NMR (C_6D_6) δ 8.49 (m, 4 H), 7.20 (m, 6 H), 6.12 (s, 20 H)) and 10% **7c**[11] (^1H NMR (C_6D_6) δ 8.49 (m, 4 H), 7.20 (m, 6 H), 6.15 (s, 10 H)).

Reaction of 3a and 4c To Produce 5c. A NMR tube experiment was performed using a previously prepared sample of **4c** (50% **4c** by NMR, 0.026 g total wt, 0.031 mmol of **4c**) and **3a** (0.012 g, 0.048 mmol) in C_6D_6. The ^1H NMR was recorded shortly afterward and the ^{13}C NMR then recorded overnight. Another ^1H NMR followed which showed partial decomposition of the sample during the night. A similarly prepared sample of **5c** was used to record the IR: ^1H NMR (C_6D_6) δ 7.70 (m, 4 H), 7.20 (m, 6 H), 6.03 (s, 20 H), 4.81 (s, 2 H), 4.11 (s, 2 H); ^{13}C NMR (C_6D_6) δ 169.6, 140.0, 130.1, 126.9, 125.5, 116.2, 86.3; IR (C_6D_6) 3235, 1615, 1445, 1320, 810, 720 cm^{-1}.

Synthesis of $\{(C_5H_5)_2Ti(OC(O)CH_3\}_2O$ (6b). To a precooled (−10 °C) Schlenk tube charged with **3a** (0.204 g, 0.822 mmol) and 2 mL of Et_2O was added $(MeCO)_2O$ (0.071 g, 0.706 mmol) via syringe. The mixture was warmed to 0 °C and stirred 80 min at which time a yellow precipitate had formed. The Schlenk tube was recooled to −20 °C and the solid collected, washed (2×, 0.5 mL, Et_2O, −20 °C), and dried under high vacuum to give 0.032 g (11% yield) of crude product: ^1H NMR (C_6D_6) δ 6.03 (s, 20 H), 2.04 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 176.7, 115.9, 24.0; IR (C_6D_6) 1640, 1364, 1300, 1015, 730 (Ti–O–Ti) cm^{-1}.

Synthesis of $(C_5H_5)_2Ti(OC(O)\text{-}t\text{-}Bu)_2$ (7a). To a Schlenk tube charged with Cp_2TiCl_2 (0.519 g, 2.09 mmol) and $NaO_2C(CH_3)_3$ (0.562 g, 4.53 mmol) was added 20 mL of toluene via syringe. The mixture was stirred for 12 h at which time it had become orange in color with no undissolved Cp_2TiCl_2. After filtration through Celite under argon the resulting clear orange solution was reduced in volume under vacuum to 10 mL and slowly cooled to −50 °C. The small orange crystals that deposited were collected, washed (2×, 0.5 mL, toluene, −50 °C) and dried under high vacuum to give 0.280 g (35% yield) of **7a**. The supernatant was evacuated to dryness to give an additional 0.133 g for an overall yield of 52%: ^1H NMR (C_6D_6) δ 6.06 (s, 10 H), 1.27 (s, 18 H); ^{13}C NMR (C_6D_6) δ 182.5, 117.7, 40.1, 28.0; IR (C_6D_6) 2945, 1645, 1481, 1395, 1294, 1188, 815 cm^{-1}. Anal. Calcd for $C_{20}H_{28}O_4Ti$: C, 63.16; H, 7.42. Found: C, 63.07; H, 7.19.

Synthesis of Chalcone (8). A Schlenk tube was charged with a previously prepared impure sample of **4c** (65% **4c** by NMR, 0.313 g total wt, 0.486 mmol of **4c**) and 2 mL of benzene added via syringe. The mixture was briefly stirred to dissolve the solid, benzaldehyde (0.140 g, 1.32 mmol) added via syringe, and the mixture stirred for 30 min at 47–49 °C. It was then allowed to cool to room temperature, 10 mL of saturated NH_4Cl (aqueous) added, and stirring continued in the air for 10 min. The organic layer was separated and washed with saturated NaCl (aqueous) (2×) and H_2O (1x), dried ($MgSO_4$), purified by filtration through silica gel, and evaporated under partial vacuum to give a yellow oil. Pentane (6 mL) was added and the solution slowly cooled to −50 °C with the appearance of white crystals. They were collected, washed (pentane, 2 ×, 0.5 mL, −50 °C), and dried under high vacuum to give 0.027 g (27% yield based on mmol of **4c**) of product: mp 55–56 °C (lit.[27] 58 °C); ^1H NMR ($CDCl_3$) δ 8.02 (m, 2 H), 7.51 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 190.5 (C=O), 144.8, 138.2, 134.8, 132.7, 130.5, 128.9, 128.4, 122.0. An independently synthesized sample[28] had identical ^1H and ^{13}C NMR spectra.

NMR Studies of Imides. Reactions were NMR tube experiments performed in C_6D_6 with the product ratios determined by integration of characteristic ^1H NMR shifts of each compound.

Chart III

compd	^{1}H NMR	^{13}C NMR
12b	7.14 (m, 5 H), 4.10 (m, 1 H), 3.88 (m, 1 H), 2.06 (m, 4 H)	
12c	7.14 (m, 5 H), 3.86 (m, 2 H), 3.80 (m, 2 H), 2.40 (s, 4 H)	152.4, 129.8, 128.8, 127.9, 127.1, 77.4, 28.4
12f	3.80 (s, 2 H), 3.76 (s, 2 H), 2.51 (s, 3 H), 2.21 (s, 4 H)	
12h	7.20 (m, 5 H), 4.16 (m, 1 H), 3.89 (m, 1 H, 2.34 (m, 3 H), 1.06 (d, J = 6.3 Hz, 3 H)	
12i	7.20 (m, 5 H), 3.84 (s, 2 H), 3.78 (s, 2 H), 2.34 (m, 3 H), 0.81 (d, J = 6.3 Hz, 3 H)	
16a	7.05 (m, 5 H), 5.43 (s, 10 H), 3.83 (t, J = 4.0 Hz, 2 H), 1.34 (s, 6 H), 0.70 (s, 3 H)	
16b	7.10 (m, 5 H), 5.50 (s, 10 H), 3.86 (s, 1 H), 3.66 (s, 1 H), ... 0.72 (s, 3 H)	
16c	7.10 (m, 5 H), 5.42 (s, 10 H), ... 0.69 (s, 3 H)	
16e	6.98 (m, 3 H), 5.44 (s, 10 H), 3.85 (t, J = 4.0 Hz, 1 H), 2.52 (t, J = 4.0 Hz, 2 H), 2.10 (s, 6 H), 2.05 (m, 2 H), 0.57 (s, 3 H)	170.7, 157.1, 137.4, 137.2, 129.7, 129.2, 113.2, 77.7, 40.6, 33.6, 19.0, 18.1
16f	7.10 (m, 5 H), 5.54 (s, 10 H), 3.55 (t, J = 4.2 Hz, 1 H), 2.05 (m, 2 H), 1.34 (s, 6 H), 0.77 (s, 3 H)	

The spectra data for the known compounds **12a,d,g,j**, **13a,b**, and **15c,j** are listed in the supplementary material. Values for the new compounds **12k,m–p**, **15a,f–i,k**, and **16d** are listed elsewhere in this section. NMR shifts of all other new compounds are listed in Chart III.

Attempted Synthesis of 3-Methyl-5-methylene-1-phenyl-2-pyrrolidinone (12h). Imide **12g** (0.175 g, 0.925 mmol) was treated in the same manner as **12j** (see below) to give 0.200 g of a yellow oil which by ^{1}H NMR was a complex mixture of products. TLC (3:1 $CHCl_3$/pet ether) also indicated many products present. Flash chromatography (3:1 $CHCl_3$/pet ether) gave only one fraction (R_f 0.70) of 0.027 g (8% yield) of a slightly yellow oil which was identified by ^{1}H and ^{13}C NMR as the known pyrrole **13c**:[30] ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 2 H), 7.10 (m, 3 H), 5.81 (s, 1 H), 1.98 (s, 3 H), 1.90 (s, 3 H), 1.82 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 139.3, 129.0, 128.0, 127.5, 127.4, 107.7, 12.7, 11.2, 10.6.

3,3-Dimethyl-5-methylene-1-phenyl-2-pyrrolidinone (12k). Imide **12j** (0.203 g, 1.00 mmol) was dissolved in 2 mL of THF and cooled to −40 °C and a solution of **1** (0.313 g, 1.10 mmol) in 3.5 mL of PhMe added dropwise over several minutes. The resulting mixture was stirred 0.5 h at −40 °C and allowed to warm to room temperature over an additional 15-min period. Workup according to Pine et al.[5] gave 0.195 g (96% yield) of crude product, mp 97–100 °C. Recrystallization (EtOH) afforded 0.090 g of pure **12k**: mp 98–101 °C; ^{1}H NMR ($CDCl_3$) δ 7.38 (m, 5 H), 4.14 (m, 2 H), 2.68 (m, 2 H), 1.31 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 180.3, 145.8, 135.3, 129.2, 127.8, 127.4, 86.2, 40.8, 40.3, 25.0. Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.39; H, 7.38; N, 6.94.

1-(3-Butenyl)-3,3-dimethyl-2,5-pyrrolidinedione (12m). 3,3-Dimethyl-2,5-pyrrolidinedione (1.30 g, 10.2 mmol)[24] was converted by the method of Mitsunobu[29] to **12m**. After flash chromatography (99:1 $CHCl_3$/THF) the resulting yellow oil was distilled under reduced pressure (bp 93 °C, 5 torr) affording 1.08 g of pure **12m** (58% yield): ^{1}H NMR ($CDCl_3$) δ 5.65 (m, 1 H), 5.04 (m, 1 H), 4.91 (m, 1 H), 3.54 (t, J = 6.8 Hz, 2 H), 2.48 (s, 2 H), 2.32 (d of t, J_1 = 6.8, J_2 = 7.1 Hz, 2 H), 126 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 183.2, 175.8, 134.5, 117.5, 43.6, 39.9, 37.6, 32.0, 25.7. Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 65.98; H, 8.27; N, 7.65.

1-(3-Butenyl)-3,3-dimethyl-5-methylene-2-pyrrolidinone (12n). Imide **12m** (0.181 g, 1.00 mmol) was treated in the same manner as **12j** (see above). Workup[5] yielded 0.200 g of crude product as a mixture of **12n,m** (2.8:1.0). **12n**: ^{1}H NMR ($CDCl_3$) δ 5.61 (m, 1 H), 5.07 (m, 1 H), 4.92 (m, 1 H), 4.21 (m, 1 H), 4.12 (m, 1 H), 3.51 (t, J = 7.2 Hz, 2 H), 2.48 (m, 2 H), 2.29 (d of t, J_1 = 6.8, J_2 = 6.9 Hz, 2 H), 1.15 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 180.9, 144.4, 134.9, 116.9, 84.2, 40.5, 39.7, 39.0, 30.9, 25.4.

3,3-Dimethyl-1-(2,6-dimethylphenyl)-5-methylene-2-pyrrolidinone (12p). Imide **12o** (0.231 g, 1.00 mmol) was treated in the same manner as **12j**, affording a quantitative crude yield of product, mp 85–87 °C. Recrystallization (EtOH) provided an analytical sample of **12p**: mp 87.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.14 (m, 3 H), 4.08 (m, 1 H), 3.79 (m, 1 H), 2.72 (m, 2 H), 2.11 (s, 6 H), 1.34 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 179.6, 143.7, 136.2, 128.4, 128.1, 85.3, 40.7, 40.3, 25.5, 17.3. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.35; H, 8.38; N, 6.04.

1-Aza-4-(formyloxy)-6,8,8-trimethylbicyclo[4.3.0]nonan-9-one (14a). A crude sample of **12n** (74% **12n** and 26% **12m** by ^{1}H NMR, 0.200 g total wt, 0.74 mmol of **12n**) was dissolved in 15 mL of HCO_2H and let stir 18 h.[14] The solution was then evaporated under reduced pressure, dissolved in 50 mL of $CHCl_3$, washed (2 × 100 mL, 5% $NaHCO_3$ (aqueous); 1 × 100 mL, H_2O), dried (Na_2SO_4), and evaporated under reduced pressure to give 0.220 g of a yellow oil. Flash chromatography (2:1 petroleum ether/acetone) afforded 0.115 g (69% yield based on starting material) of **14a** (R_f 0.38) as a slightly yellow oil. **12m** (R_f 0.74), 0.035 g, was also recovered: ^{1}H NMR ($CDCl_3$) δ 8.03 (s, 1 H), 5.22 (t of t, J_1 = 12.0, J_2 = 11.0, J_3 = J_4 = 4.4 Hz, 1 H), 4.15 (m, J_1 = 14.0, J_2 = 5.4, J_3 = 2.0 Hz, 1 H), 2.76 (t of d, J_1 = 13.0, J_2 = 14.0, J_3 = 3.0 Hz, 1 H), 2.15–1.4 (m, 4 H), 1.91 (s, 1 H), 1.89 (s, 1 H), 1.38 (s, 3 H), 1.23 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 177.5, 160.3, 68.5, 56.7, 49.7, 44.7, 40.2, 34.6, 30.8, 27.8, 27.6, 25.0. Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.73; H, 8.63; N, 5.94.

Imides 12o and 15a,f,g,h. These imides were prepared by the method of Devlin et al.[25] Yields after recrystallization or distillation were 66% (**12o**), 42% (**15a**), 55% (**15f**), 75% (**15g**), and 73% (**15h**). Melting points, spectral data, and elemental analyses for each compound are as follows.

3,3-Dimethyl-1-(2,6-dimethylphenyl)-2,5-pyrrolidinedione (12o): mp 97–98 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 7.16 (m, 3 H), 2.75 (s, 2 H), 2.10 (s, 6 H), 1.44 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 181.6, 174.3, 135.4, 130.1, 129.1, 128.3, 43.7, 40.4, 25.3, 17.4. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.53; H, 7.32; N, 6.02.

3,3-Dimethyl-1-phenyl-2,6-piperidinedione (15a): mp 115–117 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 7.40 (m, 3 H), 7.05 (m, 2 H), 2.87 (t, J = 6.9 Hz, 2 H), 1.95 (t, J = 6.9 Hz, 2 H), 1.37 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 177.7, 171.9, 135.4, 128.7, 128.0, 127.9, 38.2, 30.5, 28.4, 24.9. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87;; H, 6.96; N, 6.45. Found: C, 71.49; H, 6.84; N, 6.36.

3,3-Dimethyl-1-(2,6-dimethylphenyl)-2,6-piperidinedione (15f): mp 84–86 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 7.13 (m, 3 H), 2.89 (t, J = 6.3 Hz, 2 H), 2.02 (s, 6 H), 1.96 (t, J = 6.3 Hz, 2 H), 1.38 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 176.8, 171.2, 134.8, 128.1, 38.5, 31.0, 29.6, 25.1, 17.3. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.34; H, 7.76; N, 5.62.

1-(2,6-Dimethylphenyl)-2,6-piperidinedione (15g): mp 139–140 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 7.15 (m, 3 H), 2.83 (t, J = 6.6 Hz, 4 H), 2.10 (m, J = 6.6 Hz, 2 H), 2.07 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 171.5, 134.8, 133.3, 128.3, 128.0, 32.6, 17.3, 17.1. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87;, H, 6.96; N, 6.45. Found: C, 71.73; H, 6.95; N, 6.40.

1-Benzyl-3,3-dimethyl-2,6-piperidinedione (15h): bp 140 °C (0.5 torr); ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 5 H), 4.94 (s, 2 H), 2.73 (t, J = 7.0 Hz, 2 H), 1.80 (t, J = 7.0 Hz, 2 H), 1.27 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 177.7, 171.8, 137.3, 128.1, 127.0, 42.8, 38.2, 30.6, 29.5, 25.3. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.51; H, 7.48; N, 5.94.

1-Benzyl-3,3-dimethyl-6-methylene-2-piperidinone (15i). Imide **15h** (0.231 g, 1.00 mmol) was treated in the same manner as **12j** (see above), affording 0.261 g of a yellow oil as a mixture

of **15h,i** (1:1). Flash chromatography on silica gel (9:1 petroleum ether/acetone) gave 0.097 g (42% yield) of **15i** as a slightly yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.20 (m, 5 H), 4.93 (s, 2 H), 4.16 (s, 1 H), 4.07 (m, 1 H), 2.55 (t, J = 6.4 Hz, 2 H), 1.74 (t, J = 6.4 Hz, 2 H), 1.31 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 175.6, 144.0, 137.5, 128.3, 126.6, 126.3, 91.8, 46.4, 38.5, 34.0, 27.1, 27.0.

Reaction of 15j with "$Cp_2Ti{=}CH_2$" Sources (results presented in Table III). In runs 1–5, **15j** was dissolved in 1 mL of PhMe, 0.1 mL of pyridine added, and the mixture stirred at the desired temperature. 1 (in 6 mL of PhMe) was added dropwise over 5 min and stirring continued for 0.5 h at temperature listed and an additional 0.25 h without temperature bath. Workup[5] gave a quantitative yield of **15k** and unreacted **15j** as a yellow oil. ^{1}H NMR integration gave percent yield of **15k**. In runs 6 and 7 THF was used in place of PhMe while in run 8 the imide was dissolved in THF and 1 in PhMe. Runs 9–11 were NMR tube experiments. Spectral data of **15k**: ^{1}H NMR ($CDCl_3$) δ 4.21 (s, 1 H), 4.12 (m, 1 H), 3.12 (s, 3 H), 2.56 (t, J = 6.4 Hz, 2 H), 1.69 (t, J = 6.4 Hz, 2 H), 1.24 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 176.3, 145.7, 90.4, 38.5, 34.5, 34.4, 27.0, 26.7.

The Titanium Enolate of 3,3-Dimethyl-1-(2,6-dimethylphenyl)-2,6-piperidinedione (16d). To a Schlenk tube charged with **3a** (0.085 g, 0.34 mmol) and **15f** (0.095 g, 0.35 mmol) was added 2 mL of PhMe via syringe. The resulting mixture was stirred 0.5 h with the formation of a bright orange precipitate. Additional PhMe was added (7 mL) to give a clear orange solution which was slowly cooled to −50 °C. Isolation of the resulting orange crystals gave 0.065 g (44% yield) of **16d**: ^{1}H NMR (C_6D_6) δ 6.96 (m, 3 H), 5.47 (s, 10 H), 3.81 (t, J = 4.5 Hz, 1 H), 2.13 (d, J = 4.5 Hz, 2 H), 2.10 (s, 6 H), 1.34 (s, 6 H), 0.58 (s, 3 H); ^{13}C NMR (C_6D_6) δ 173.8, 155.8, 137.7, 137.1, 129.6, 129.4, 113.1, 76.0, 40.6, 38.1, 34.4, 25.2. Anal. Calcd for $C_{26}H_{31}NO_2Ti$: C, 71.39; H, 7.14; N, 3.20. Found: C, 71.25;, H, 7.11;, N, 3.18.

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Registry No. 1, 67719-69-1; **2**, 83876-46-4; **3a**, 80122-07-2; **3b**, 75687-68-2; **4a**, 96326-46-4; **4b**, 96326-47-5; **4c**, 96326-48-6; **5b**, 96326-49-7; **5c**, 96326-50-0; **6b**, 96326-51-1; **6c**, 96326-52-2; **7a**, 96326-60-2; **7b**, 1282-51-5; **7c**, 12156-48-8; **8**, 94-41-7; **9**, 96348-34-4; **10**, 96348-35-5; **12a**, 83-25-0; **12b**, 96326-28-2; **12c**, 96326-29-3; **12d**, 1121-07-9; **12e**, 50782-57-5; **12f**, 96326-30-6; **12g**, 75619-07-7; **12h**, 96326-31-7; **12i**, 96326-32-8; **12j**, 6144-75-8; **12k**, 96326-33-9; **12l**, 96326-34-0; **12m**, 96326-35-1; **12n**, 96326-36-2; **12o**, 96326-37-3; **12p**, 96326-38-4; **13a**, 83-24-9; **13b**, 930-87-0; **13c**, 70319-57-2; **14a**, 96348-31-1; **15a**, 96326-39-5; **15b**, 96348-32-2; **15c**, 5768-13-8; **15d**, 96326-40-8; **15e**, 96326-41-9; **15f**, 96326-42-0; **15g**, 96326-43-1; **15h**, 96326-44-2; **15i**, 96348-33-3; **15j**, 1195-95-5; **15k**, 96326-45-3; **16a**, 96326-53-3; **16b**, 96326-54-4; **16c**, 96326-55-5; **16d**, 96326-56-6; **16e**, 96348-36-6; **16f**, 96326-57-7; **17**, 96326-58-8; **18**, 96326-59-9; $(PhCO)_2O$, 102-09-0; Cp_2TiCl_2, 1271-19-8; $NaO_2CC(CH_3)_3$, 1184-88-9; $(Cp_2T_1{=}O)_n$, 59487-89-7; pivalic anhydride, 1538-75-6; acetic anhydride, 108-24-7; benzaldehyde, 100-52-7; phthalic anhydride, 85-44-9; glutaric anhydride, 108-55-4; pinacolone, 75-97-8; 3,3-dimethyl-2,5-pyrrolidinedione, 3437-29-4.

Supplementary Material Available: ^{1}H NMR data for **12a,d,g,j**, **13a,b**, and **15c,j** (1 page). Ordering information is given on any current masthead page.

Synthesis of the Dolastatin Thiazole Amino Acid Component (gln)Thz[1]

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The new thiazole amino acid (gln)Thz, found to occur as one unit of the marine sea hare cyclic pentapeptide dolastatin 3, has been synthesized from L-glutamic acid by the route **2** → **10e**. The synthesis of Z-L-isoglutamine (**4**) was improved by selective ammonolysis of anhydride **3** at −60 °C. A variety of reaction conditions were found to cause complete racemization during the Hantzsch thiazole synthesis step (**9** → **10**). Deuterium labeling experiments indicated loss of the chiral center prior to formation of the thiazole system and suggested an imine–enamine type equilibration involving intermediates A ⇌ B (Scheme II). The *N*-benzyloxycarbonyl derivative (**10d**) of (gln)Thz was partially resolved by employing brucine.

Until discovery of the marine Mollusca (sea hare)[2,3] and Urochordata (tunicate)[4] thiazole cyclic peptides such interesting amino acid structural units[5,6] were only known in *Streptomyces* antibiotics of the thiostrepton[7] and nosiheptide[8] types. Only a few natural thiazole amino acids have been prepared by synthesis.[9,10] These earlier studies were primarily concerned with Gly, Ala, and Val conversions to (gly)Thz (**1a**),[2] (ala)Thz (**1b**), and (val)Thz (**1c**) needed in part for thiostrepton structural efforts.[9] Preparatory to further structural investigations and total syntheses of the potent cell growth inhibitor (P388 lymphocytic leukemia cell line) dolastatin 3[2] and related dolastatins[3] from the sea hare *Dolabella auricularia* we began

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