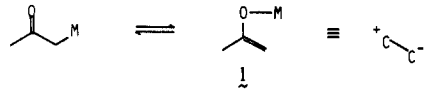
Trichlorotitanium and Alkoxytitanium Homoenolates. Preparation, Characterization, and Utilization for Organic Synthesis

Eiichi Nakamura,* Hiroji Oshino, and Isao Kuwajima*

Contribution from the Department of Chemistry, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan. *Received September 5, 1985*

Abstract: The reaction of 1-alkoxy-1-siloxycyclopropanes (e.g., **4**, **10**, **11**) with $TiCl_4$ gives deep purple, crystalline 3-trichlorotitanium propionates (e.g., **5**, **12**) in good yield. These compounds are highly thermally stable due to the five-membered chelate structure, which has been elucidated by spectral studies. An alkoxytitanium species generated by treatment of **5** with half an equivalent of a tetraalkoxytitanium is more reactive than **5**, providing efficient synthetic routes to 4-hydroxy esters (homo-Reformatsky reaction), γ-lactones, and cyclopropanecarboxylates. The mechanisms of the homoenolate formation reactions are discussed.

The value of enolate anion **1**, one of the most important reactive species in organic chemistry, stems mainly from its amphoteric nature (eq 1). In this same sense, homoenolate[1] **2** has at least an equal potentiality but has not received due attention thus far. One of the reasons for the lack of interest in the past[2] is that the reactive homoenolate anions (e.g., **2**: M = Na, Li)[3,4] spontaneously cyclize to cyclopropane tautomer **3**, which then reacts as a simple alkoxide toward various electrophiles.[2] The previous chemistry of the homoenolate has therefore been centered only on the least reactive of the class, e.g., M = Hg[5] and Sn.[6] Lack of a reasonably general preparative method was another factor which impeded the studies about homoenolate chemistry. Action of a base upon a carbonyl compound generates an enolate anion but does not generate its homologue, since the carbonyl group lowers the pK_a value of the β-hydrogen only very slightly.[2]



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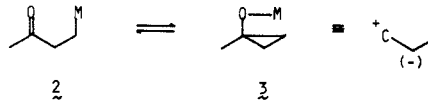
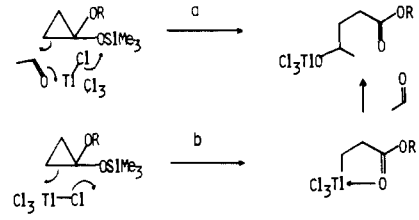


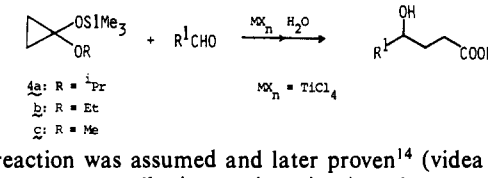
(2)

Synthetic chemists have overcome these problems by developing suitable "synthetic equivalents". The basic concept involved in the designing of such "equivalents" generally relied on masking of the carbonyl group to make a single nucleophilic site β to the original carbonyl function.[7,8] A related approach via temporary anionic protection of the carbonyl group, by generating dianions, has been pioneered by Caine[9] and recently propagated by Goswami.[10,11]

Scheme I



The last several years have seen development of an entirely new research area in which the metal homoenolate itself is prepared, usually from siloxycyclopropanes,[12] and used for carbon–carbon bond formation. The initial success in this field was recorded by us for the $TiCl_4$-mediated coupling of the siloxycyclopropane **4** with carbonyl compounds ("homo-Reformatsky reaction") (eq 3).[13]



(3)

This reaction was assumed and later proven[14] (videa infra) to involve a structurally interesting titanium homoenolate, the chemistry of which is the subject of the present paper. A number of other metal homoenolates,[15a] inter alia, zinc homoenolate of

(1) Because of the general lack of concern about the chemistry of metal homoenolates (except their synthetic equivalents), the word "homoenolate" has been related only loosely to the carbon anion **2**. Etymologically, however, this word is related more to the oxygen anion **3**, similar to the case of "enolate". In spite of such formalism, we prefer using "metal homoenolate" as the term for **2**; for **3** may more commonly be referred to as cyclopropanolate and usually behaves as such.[3,4] The initial use of the term "homoenolate" for the carbanion **2** has been made by the pioneer of this chemistry (Nickon, A.; Lambert, J. L. *J. Am. Chem. Soc.* **1962**, *84*, 4604.

(2) Reviews: Werctiuk, N. H. *Tetrahedron* **1983**, *39*, 205. Ryu, I.; Sonda, N. *J. Syn. Org. Chem., Jpn.* **1985**, *43*, 112.

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Table I. NMR Spectra of Titanium Homoenolates[a]

entry	homoenolate	^{1}H NMR (60 MHz) C-2	C-3	others	^{13}C NMR (22.25 MHz) C-1	C-2	C-3	others
1	**5a**	2.40 (t:7)	3.38 (t:7)	1.51 (d:6) 5.65 (qq:6,6)	189.8	44.1	100.6	21.6, 77.7
2	**5b**[c]	2.73 (t:7)	3.37 (t:7)	1.54 (d:7) 4.71 (q:7)				
3	**5a** + benzophenone	2.70 (t:7)	3.28 (t:7)	1.40 (d:6) 5.20 (qq:6,6)				
4	**24**[d]	1.88 (t:7)	3.03 (t:7)		189.4	40.0	86.8	(21.6, 24.6) 75.4

[a] The chemical shift values and the splitting patterns showed moderate concentration dependence. Numbers in parentheses are coupling constants in Hz. Solvent was $CDCl_3$ unless noted. [b] $W_{1/2}$ = ca. 45 Hz on proton noise decoupling. [c] Solvent was CCl_4. [d] The dialkoxydichlorotitanium formed along with **24** (eq 10) was not removed.

Table II. IR Spectra of Titanium Homoenolates

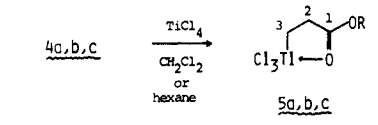
entry	homoenolate	solvent	absorption (cm^{-1})[a]								
1	**5a**	KBr	1610 br s	1465 m	1390 sh	1375 m	1325 s	1095 s	880 br	360 br	
2		0.1 M benzene	2930 s	1603 vs	1425 s	1330 m	1325 s	1095 s	895 m	800 m	
3		0.02 M CCl_4	1608 vs								
4	**5a** + acetone	0.1 M benzene	2940	1675 vs	1605 vs	1420	1375	1325	1240	1090	
5	**5a** + benzophenone	0.02 M CCl_4	2960	1627	1330	1280	1100				
6	**5** + 2,2′-bipyridine	KBr	1725	1585	1465	1440	1315	1200	1015	765	725
7	**12a**	0.1 M $CDCl_3$	2970 m	2940 m	1595 vs	1460 w	1429 w	1320 m	1250 m	1090 m	882 m

[a] Abbreviations: vs, very storng; s, strong; m, medium; w, weak; br, broad.

esters, have subsequently been prepared and used for various synthetic reactions.[15] Significant contribution to the chemistry of *ketone* homoenolates has been made by the group at Osaka.[16] Homoenolate-type radicals[17] are also interesting reactive species. A synthetic merit of this new chemistry resides in omission of the masking/unmasking procedure required by the "synthetic equivalents" approach. More significant virtue of such endeavor chemistry, however, is that it provides important insights into the nature of the homoenolate,[15d] about which much still remains to be found.

As mentioned above, our investigation about the role of siloxycyclopropanes as a precursor to the homoenolates was initiated by the reaction of **4** with carbonyl compounds in the presence of $TiCl_4$ (eq 3).[13] Two possible mechanisms for this reaction have been considered (Scheme I): one involves direct electrophilic attack of a strongly polarized carbonyl group onto the cyclopropane ring (path a), and the other assumes intermediacy of a titanium homoenolate (path b). The former possibility had a well-established prototype in the chemistry of *enol* silyl ethers.[18,19] Several experimental observations, however, led us to believe that the reaction proceeds via the second pathway. A notable result from the quest in this line was the isolation of the postulated titanium homoenolates,[14] the first characterizable nucleophilic species possessing a homoenolate structure. This article describes various aspects of the homoenolate-forming reaction and also the synthetic utilities of the resulting titanium homoenolates.

Isolation of Trichlorotitanium Homoenolates. Trichlorotitanium alkyls are usually red in color.[20] We therefore conjectured that the deep red color which develops at the start of the $TiCl_4$-mediated reaction of the siloxycyclopropane **4** (eq 3)[13] is due to a titanium homoenolate. Isolation of a 3-stannylpropionate[15a] during preliminary studies provided an encouragement. Our serious concern was about the expected instability of the desired titanium complex.[20]



(4)

After experimentation under various conditions, an unexpectedly straightforward preparation of the long-sought homoenolate was found. Thus, addition of isopropyl ether **4a** to a solution of $TiCl_4$ in $CDCl_3$ at room temperature almost instantaneously (90% conversion after ca. 2 min, 35 °C) gave a wine-red solution, in which the homoenolate **5a** and Me_3SiCl had formed in 89% and 100% ^{1}H NMR yield, respectively (eq 4). The reaction of the ethyl ether **4b** gave a slightly lower yield (83%). A second equivalent of the cyclopropane failed to introduced another propionate moiety to **4b**. Methyl ether **4c** gave a thermally stable methyl ester **5c** in an even lower yield (70%). The reaction occurs smoothly in the presence of a small amount of moderately basic compounds such as a ketone but does not proceed in ethereal solvents that bind strongly with $TiCl_4$. No reaction took place when $TiCl_4$ was replaced by $TiCl_3$.

Hexane is a particularly suitable solvent for the preparation of the homoenolates in that the product precipitates as it is formed. Thus, addition of **4a** to a solution of $TiCl_4$ (1 equiv) in hexane at room temperature gave a milky suspension for a short moment, which then turned into a deep brown solution with evolution of heat, and the titanium homoenolate **5a** crystallized out as fine purple needles in a few minutes. Removal of the brown supernatant followed by repeated washing with hexane gave the homoenolate in about 90% yield. The supernatant contained a theoretical amount of Me_3SiCl. Recrystallization from chloroform/hexane gave an analytically pure compound.

The structure of the organic portion of the titanium complex was unambiguously determined by its spectral properties (Tables I and II). The ^{1}H and ^{13}C NMR spectra (Table I, entry 1) indicated the presence of two *nonequivalent methylene signals* assignable to C-2 and C-3 (for numbering, see **5**), precluding the alternative (symmetrical) cyclopropanolate structure (cf., **4**). Assignment of these NMR signals was made with the aid of the selective proton noise decoupling technique and was confirmed

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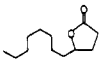
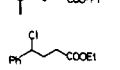
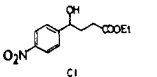
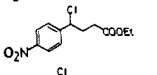
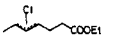
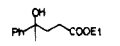
Table III. The Reaction of Trichlorotitanium Homoenolate **5a,b**[a]

entry	aldehyde	5	condns temp (°C), time (h)	product	% yield
1	nonanal	**5b**	0, 1		81
2	2-methylbutanal	**5a**	20, 6		79
3	2-phenylpropanal	**5a**	0, 2.5		67 (85:15)[b]
4	benzaldehyde	**5b**	0, 1.5		90
5	*p*-nitrobenzaldehyde	**5b**	0, 2		41[c]
6	*p*-nitrobenzaldehyde	**5b**	21, 6		100
7	crotonaldehyde	**5b**	0, 1.5		83
8	acetophenone	**5b**	0, 1		31[d]

[a] See Table I in Supplementary Material for details. [b] Ratio of **26**:**27**. [c] Starting aldehyde was recovered (60%). [d] Starting ketone was recovered (43%).

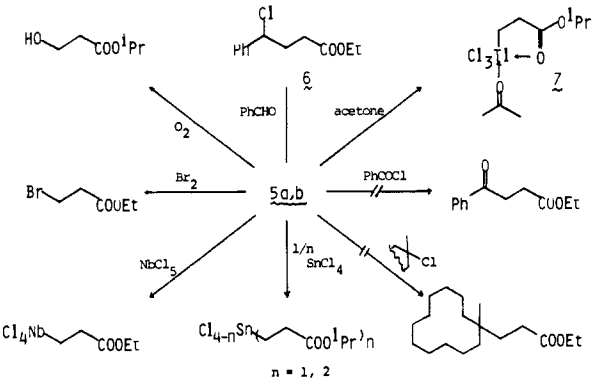
by spectral comparison with the methyl-substituted homoenolate (**12a**, vide infra). The ^{13}C NMR spectrum exhibited a characteristic very low field signal of the C-3 carbon bound to the metal atom, broadened presumably by the effect of nuclear quadrupole (Table I, entry 1). The C=O stretching band in the IR spectrum consistently appeared at ca. 1600 cm^{-1} at various concentrations in CCl_4 up to 0.02 M (Table II, entries 1–3), indicating a chelate structure shown. The downfield shift of the carbonyl carbon (as compared with simple alkyl esters) is also in accordance with the chelate structure. Such spectral properties closely resemble those of the alkyl 3-(trichlorostannyl)propionate, whose chelate structure has been elucidated by X-ray analysis.[6] The internal coordination of the ester group to the metal remains intact in the presence of a weakly basic compound such as benzene (1603 cm^{-1}) or ketones (1605 cm^{-1}) (Table II, entries 4 and 5). A more powerful ligand, 2,2′-bipyridine, gave a deep blue complex, which showed a band at 1720 cm^{-1} (entry 6).

The titanium homoenolate, while sensitive to oxygen and moisture, proved to have exceedingly high thermal stability. The homoenolate **5a** remained unchanged on a shelf in an evacuated ampule for some months and decomposed in solution (26 °C, 0.1 M in benzene) with a half-life of 4 months! It melts at 90–95 °C with color change to reddish brown and sublimes under vacuum (0.005 mmHg) at 90–110 °C. In view of the fact that an uncoordinated alkyltitanium trihalide is so unstable that none of the long chain alkyl derivatives have been prepared,[20] the behavior of **5** is astonishing. Undoubtedly, the internal ester ligand endows the carbon–metal bond with such extraordinary properties.[21]

The chemical reactivities of the titanium homoenolate are similar to the ordinary titanium alkyls (Scheme II). Oxidation of the metal–carbon bond with bromine or oxygen occurs readily to give the expected brominated or hydroxylated products in high yield. The propionate moiety was smoothly transferred to $NbCl_5$, but not to $AgCl_3$, being in line with the known order of ligand transfer.[22] Unlike $MeTiCl_3$ which permethylates $SnCl_4$,[22] the titanium homoenolate alkylated $SnCl_4$ only twice. The first equivalent of the titanium alkyl reacted rapidly at room temperature to give the monoalkyl tin, and the second equivalent slowly afforded the dialkylated compound. The enhanced thermal stability due to internal chelation appears to be balanced by the relatively low reactivities of the homoenolate complex.

Also in Scheme II the reactions with organic electrophiles are summarized. The reaction with benzaldehyde as monitored by ^1H NMR (CCl_4) indicated the formation of a coupling product

Scheme II



in a minute and gradual production of 4-chloro ester **6** (80% yield after 4 h). Chlorination of the initial adduct was expected from our previous experience.[13] Ketones did not undergo the desired C–C bond forming reaction. Reaction of the homoenolate **5a** and 1 equiv of acetone in benzene gave, with color change of the solution from brown to purple, a 1:1 addition complex, whose molecular weight determined by cryoscopy was 310. In the IR spectrum (0.1 M in benzene) of the complex in solution were found all the characteristic bands of the titanium homoenolate only slightly perturbed, in addition to a carbonyl band due to acetone coordinated to the metal center (Table II, entry 6), suggesting a hexacoordinated monomeric structure **7**. Benzophenone also formed a complex (Table I, entry 3; Table II, entry 7) which is less stable than the parent titanium alkyl and decomposed in a period of a week at 25 °C in $CDCl_3$, leaving the ketone intact. In contrast to the zinc homoenolate,[15d] the titanium homoenolate is inert to benzoyl chloride, or even to a benzoyl chloride/$AlCl_3$ complex. No significant change of ^1H NMR spectrum was induced by these acylating reagents in $CDCl_3$. The homoenolate **5b** did not react with a *tert*-alkyl chloride, with which, however, methyltitanium trichloride reacts.[23]

Table III summarizes the reaction with carbonyl compounds. Adducts formed from aliphatic aldehydes may be isolated either as a 4-hydroxy ester after neutral workup (entries 3, 5, and 8) or as a lactone by acidic workup (entries 1 and 2). Aromatic and unsaturated aldehydes usually gave chlorinated esters (entries 4, 6, and 7).

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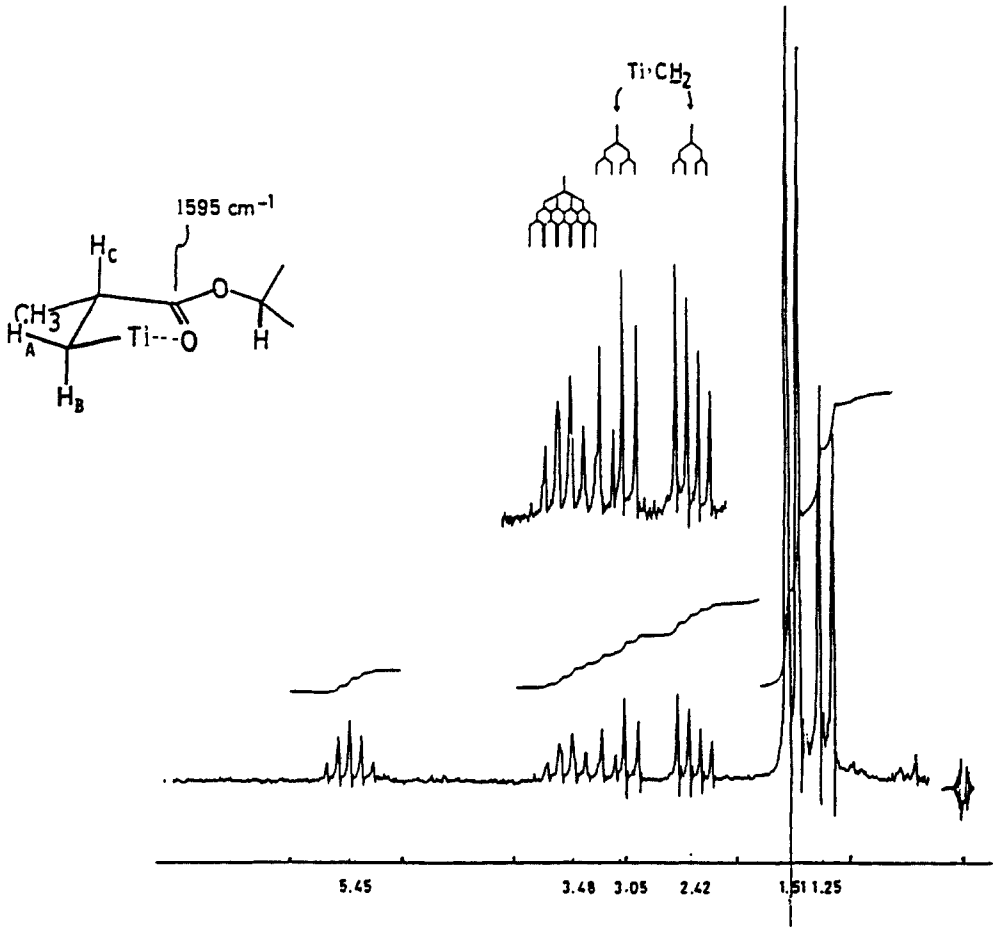
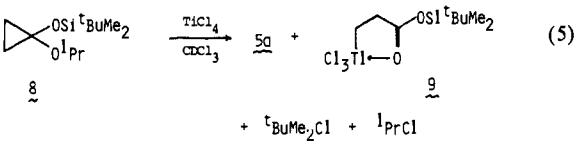


Figure 1. 60-MHz ^{1}H NMR spectrum of titanium homoenolate **12a**.

Regiochemistry of the Ring Cleavage. The reaction of (*tert*-butyldimethylsiloxy)cyclopropane **8** resulted in an unexpected consequence: This substrate gave the expected **5a** and the *tert*-butyldimethylsilyl ester **9** in equal quantity (as well as *tert*-butyldimethylsilyl chloride and isopropyl chloride; eq 5). The mechanistic significance of these results will be discussed later.

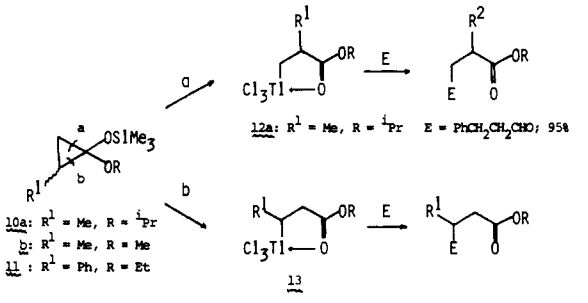


(5)

The reaction of a 2-substituted cyclopropane derivative such as **10** poses regiochemical problems in that it can afford products due to ring cleavage either at a less (path a) or a more (path b) substituted position (Scheme III). It is known that cyclopropanol reacts with Hg(II) salts predominantly via the former when the substituent is methyl and via the latter when phenyl.[24]

The reaction of the methylcyclopropane **10a** (cis:trans = 1:1) with $TiCl_4$ in $CDCl_3$ afforded a complex mixture containing only the 2-methyl-substituted complex **12a** (45% NMR yield). That none of the structural isomer **13** existed in the crude mixture was confirmed by quenching of the crude solution with bromine that produced no trace of isopropyl 3-bromobutyrate. The reaction of the corresponding methyl ether **10b** was more complex (ca. 20% yield). The homoenolate **12a** was isolated as thermally stable purple crystals (55% crude yield) by the reaction performed in hexane. The IR spectrum showed again a chelated carbonyl stretching band (1595 cm^{-1}; Table II, entry 7). Orientation of the methyl group in the five-membered chelate was deduced by analysis of the ^{1}H NMR spectrum (Figure 1). A part structure constructed from the coupling constants among $H_{a,b,c}$ indicated

Scheme III



the equatorial orientation of the methyl group in the chelated five-membered ring. The titanium complex **10a** reacted with 3-phenyl-propanal to give the expected adduct, 6-phenyl-4-hydroxy-2-methylhexanoate, in 95% yield (Scheme III).

Although these findings appeared to indicate a highly regioselective ring opening, the low yield of **12a** made us suspect that the product **13** (R^1 = Me) due to an alternative ring cleavage, being a secondary alkyl titanium, escaped detection because of its thermal instability.[26b] Attempts to trap the 3-methyl isomer **13** as its oxygenated product by carrying out the reaction of the methylcyclopropane **10a** under oxygen atmosphere failed. Trapping with aldehydes, however, revealed the formation of the elusive homoenolate **13**. When **10b** was allowed to react with a preformed 3-phenylpropanal/$TiCl_4$ complex at 0 °C in methylene chloride, a 61:39 mixture of α-methyl- and β-methyl-substituted

(24) Gibson, D. H.; DePuy, C. H. *Chem. Rev.* **1974**, *74*, 605.
(25) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1985**, *107*, 2138.

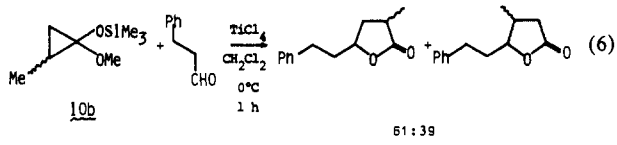
(26) (a) Reviews: Reetz, M. T. *Top. Curr. Chem.* **1982**, *106*, 1. Seebach, D. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Otto Salle Verlag: Frankfurt, 1983; Vol. 3, p 217. (b) Weidmann, B.; Maycock, C. D.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 1552.
(27) Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041. Tyrlik, S.; Wolochowicz, I. *Bull Soc. Chim. Fr.* **1973**, 2147. McMurry, J. E. *Acc. Chem. Res.* **1974**, *7*, 281.

Table IV. Alkoxide Modification of the Titanium Homoenolate[a]

$M(OR)_n$, equiv		% yield 20	% yield 21
LiOMe	1.0	0	82
LiOMe	2.0	0	52
LiOMe	3.0	0	36
LiO-*i*-Pr	3.0	0	32
LiO-*t*-Bu	3.0	0	24
$Mg(OMe)_2$	1.5	0	25
$Ti(O\text{-}i\text{-}Pr)_4$	0.5	90	0

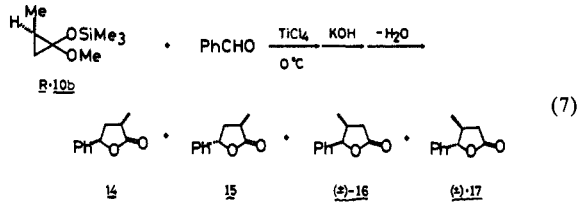
[a] See Experimental Section for conditions.

lactones was formed (eq 6). The addition reaction was only marginally diastereoselective, producing the α-methyl isomer in a 1:1 ratio and the β-isomer in a 2:1 ratio.



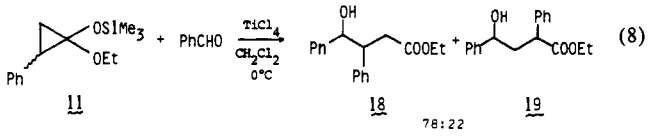
(6)

In order to further probe the mechanism of the ring cleavage, an element of chirality was introduced to the cyclopropane (eq 7). The cyclopropane (*R*)-**10b** was prepared by reductive cyclization of methyl (*R*)-3-bromo-2-propionate as a 1:1 mixture of epimers at C-1. The expectation was that analysis of the absolute stereochemistry of the chiral centers formed in **16** and **17** would give useful information about the chirality in the secondary alkyl titanium **13** (R^1 = Me) which in turn would show the mechanism of the ring cleavage reaction. Thus, the chiral cyclopropane was allowed to react with benzaldehyde/$TiCl_4$ complex for 15 min at 0 °C in methylene chloride, the crude hydroxy ester hydrolyzed with aqueous KOH, and the resulting potassium carboxylate lactonized with 2-chloropyridine methiodide. The crude product consisted of a 29:32:28:11 of *cis*-α-, *trans*-α-, *cis*-β-, and *trans*-β-methyl isomers. The relative stereochemistry of these isomers was determined by comparison with authentic samples (see Scheme VIII and Experimental Section). This product ratio was in good agreement with that observed with 3-phenylpropanal (eq 6). The optical purity of each isomer was determined by a chiral europium shift reagent: While the α-methyl isomers largely retained the chirality (in spite of the possible racemization via enolization), *the β-methyl isomers completely lost the chirality.*



(7)

Phenylcyclopropane **11** (cis:trans = 6:4) failed to give any characterizable titanium alkyls upon reaction with $TiCl_4$ in hexane, but in situ trapping with benzaldehyde afforded the expected adduct in good yield as a 78:22 mixture of **18** and **19**, indicating preferential cleavage at the more substituted position (eq 8). The diastereoselectivity observed for **18** was 90:10.



(8)

Alkoxide-Modified Homoenolate. From the current standard of organic synthesis, there remained much to be desired for the trichlorotitanium homoenolates as a synthetic reagent, in particular, as to their low nucleophilicity and the propensity to give chlorinated products (cf. Table III). Considering the electron-withdrawing properties of the chlorine atoms attached to the metal, we envisioned that replacement of these with alkoxides would make the homoenolate more synthetically useful.

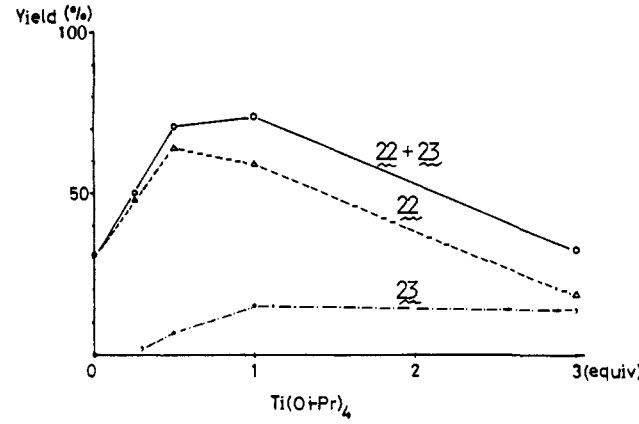
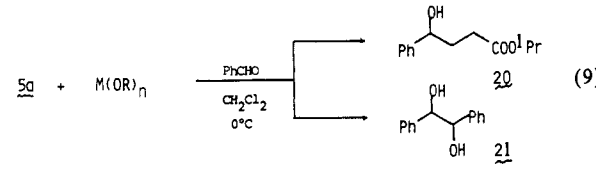


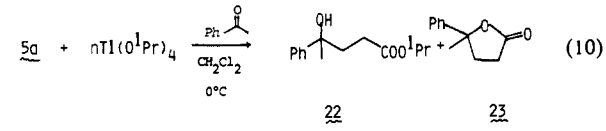
Figure 2. Dependency of the yield of **22** and **23** upon the amount of $Ti(O\text{-}i\text{-}Pr)_4$ added to **5a** (eq 10).

Ligand exchange reaction was examined in the addition reaction of **5a** with benzaldehyde (eq 9, Table IV). To our surprise, **5a** treated with lithium and magnesium alkoxides exclusively produced the pinacol **21**. Apparently, the excessive basicity of these alkoxides had caused the formation of low-valent titanium via a β-elimination reaction.[26] Less basic $Ti(O\text{-}i\text{-}Pr)_4$, on the other hand, gave the desired 4-hydroxy ester **20** and none of the chlorinated product.



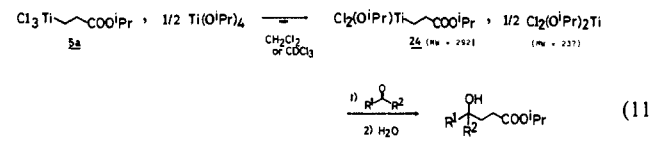
(9)

The alkoxide also enhances the nucleophilicity of the homoenolate as shown in the reaction with acetophenone at 0 °C (eq 10). The yield of the adducts (**22** and **23**) against the amount of $Ti(O\text{-}i\text{-}Pr)_4$ added (*n* equiv) is plotted in Figure 2. The yield increased steadily until *n* reached 0.5, the stoichiometry suggesting the formation of a new reactive homoenolate, monoalkoxydichlorotitanium homoenolate **24**.



(10)

The *n*-dependent change of the ^1H NMR spectrum was then studied (Figure 3). Upon addition of a small amount of the alkoxide, extensive broadening of the CH_2Ti signal was noticed, indicating occurrence of a rapid equilibrium(s) involving at least two different homoenolate species. The signals then sharpened again as *n* reached 0.5, showing that a homogeneous species was then formed. The $CH_2C{=}O$ signal (Figure 4) also broadens at n = 0–0.5. Addition of more than 1 equiv of the alkoxide caused the weakening of the homoenolate signals. A plot of the chemical shift values (Figure 5) showed an apparent change of the slope also at n = 0.5. Cryoscopic measurements of the mixtures (n = 0.5 in benzene) showed molecular weights of 360 ± 10, indicating significant contribution of monomeric titanium species. The ^{13}C NMR spectrum of the reactive homoenolate mixture (n = 0.5) exhibits the C-3 methylene carbon at a field much higher (86.8 ppm) than that of **5a** (Table I, entry 4), being in line with the higher reactivities of the new species. The role of dialkoxydichlorotitanium, formed along with **24**, in the 1,2-addition reaction is yet to be determined.



(11)

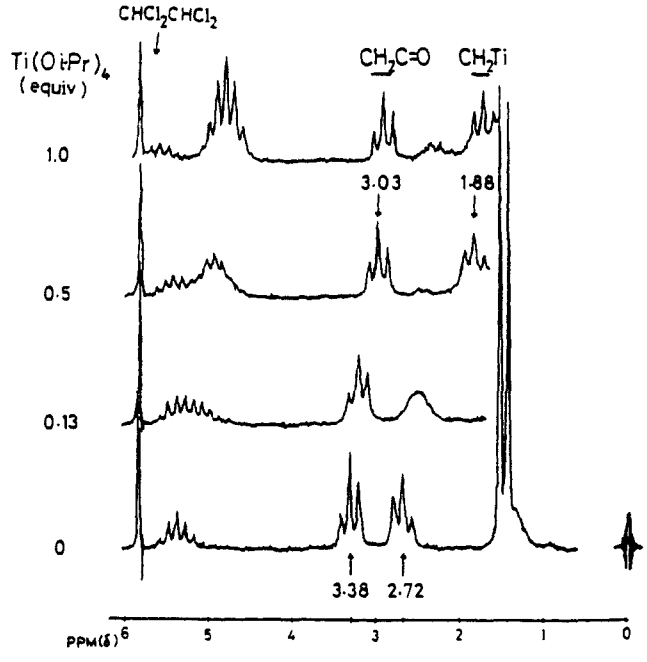


Figure 3. 60-MHz ^{1}H NMR spectra of a mixture of **5a** + Ti(O-*i*-Pr)$_4$ (eq 11).

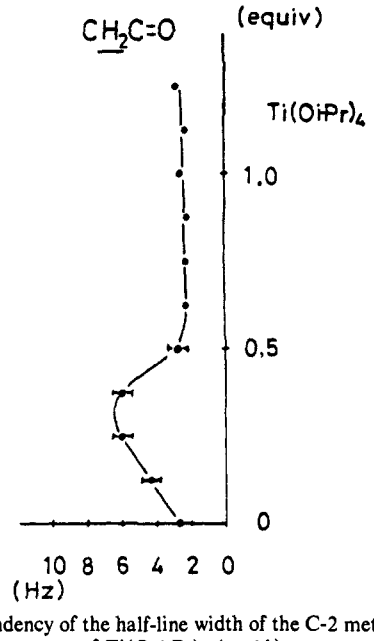


Figure 4. Dependency of the half-line width of the C-2 methylene proton signal upon the amount of Ti(O-*i*-Pr)$_4$ (eq 11).

Table V indicates readily discernible enhancement of the reactivity of the homoenolate by the isopropoxide addition, showing that it now adds to aliphatic ketones to give lactones. The addition onto aldehydes is rapid enough to permit isolation of the 4-hydroxy esters (in particular, with isopropyl esters). Despite the well-known ability of titanium alkoxides to effect ester exchange, none of this side reaction occurred under the present low-temperature conditions (e.g., obtention of an ethyl ester from the ethoxycyclopropane **4b**). While the use of (commercially available) Ti(O-*i*-Pr)$_4$ offered a fair solution to the aforementioned problems, subsequent examination of various ketones soon revealed that a more powerful ligand modification was needed (cf. Table V, entry 8).

We therefore examined several other alkoxide ligands. Phenoxide was ineffective. The polymeric nature of the required titanium alkoxides hampered the use of an ethylene glycol ligand. Further enhancement of the nucleophilicity was eventually attained with *tert*-butoxide modification of the complex (eq 12). With this was found particular improvement for ketonic substrates. Table VI shows the results. In this most refined form, the titanium homoenolate provides an extremely efficient entry to γ-lactones. In addition, by the reaction at low temperatures 4-hydroxy esters can also be isolated (e.g., entries 1 and 12).

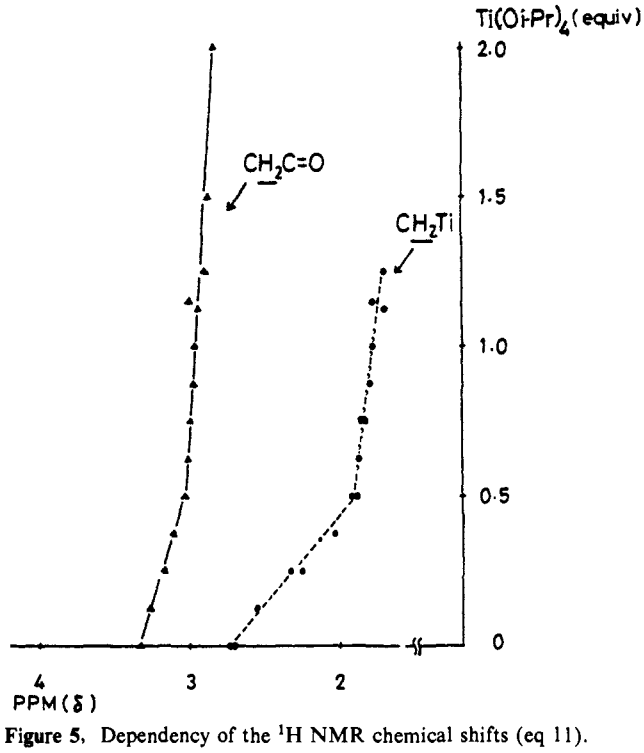
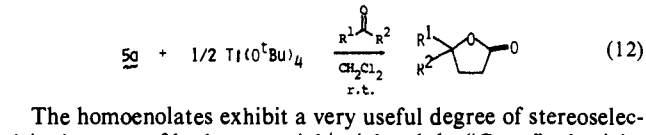


Figure 5. Dependency of the ^{1}H NMR chemical shifts (eq 11).

Table V. The Reaction of the Isopropoxide-Modified Homoenolate (eq 10)[a]

entry	carbonyl compd	condns temp (°C), time (h)	% yield
1	benzaldehyde	0, 1	90
2	*p*-nitrobenzaldehyde	0, 0.8	97
3	piperonal	0, 0.5	79
4	cinnamaldehyde	0, 1	53
5	crotonaldehyde	0, 0.03	88
6	3-phenylpropanal	0, 0.5	59
7	acetophenone	20, 1	66 + 12[b]
8	3-pentanone	20, 18	61[b,c]
9	cyclohexanone	20, 1	62[b]

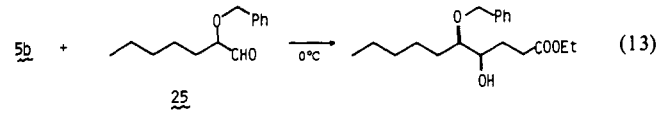
[a] The adduct was isolated as a 4-hydroxy ester. [b] The product was isolated as a γ-lactone except those indicated. [c] About 10% of 4-chloro ester formed.



The homoenolates exhibit a very useful degree of stereoselectivity in terms of both equatorial/axial and the "Cram" selectivity (Table VII, entries 1 and 2). Interestingly, the titanium homoenolates behave similarly to simple titanium alkyls[26] (entries 3 and 4) and not like the structurally related dilithio homoenolate (entry 5),[9] which in turn reacts like simple metal alkyls (entries 6–10).[28] The reaction of the titanium homoenolate **5b** with 2-benzyloxyaldehyde **25** at 0 °C predominantly (79% selective) gave the product due to presumed "chelation control".[28b] Me_3SiCl-catalyzed reaction of zinc homoenolate with **25** was more stereoselective (93%).[15d]

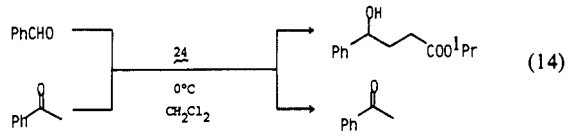
The chemoselectivity of the alkoxide-modified homoenolate (eq 13) also recalls the properties of simpler titanium alkyls. Thus, when a equimolar mixture of benzaldehyde and acetophenone was

(28) (a) Review: Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 251. (b) Review: Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*; Prentice Hall: New Jersey, 1973. (c) Nakamura, E.; Horiguchi, Y.; Shimada, J.; Kuwajima, I. *J. Chem. Soc., Chem. Commun.* **1983**, 796.



(13)

treated with 1 equiv of the isopropoxide-modified homoenolate, the addition took place specifically (97%) on the aldehyde, leaving the ketone intact. The conspicuously slower rate of addition onto 2-methylcyclohexanone (Table VI, entry 9) than to other cyclohexanone derivatives (entries 8, 10, and 11) indicates the sensitivity of the homoenolate toward steric hindrance (see also entries 4 and 5).



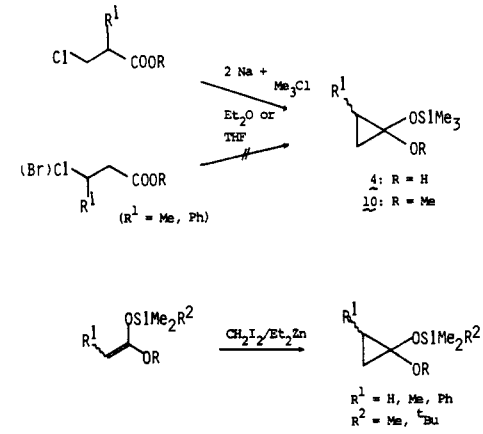
(14)

Preparation of the starting cyclopropanes is described briefly at this point (Scheme IV). The archetypal cyclopropanes **4a,b,c** were synthesized very conveniently on a large scale by reductive silylation of alkyl 3-chloropropionates.[4] The same method applies also to the preparation of the methylcyclopropane **10** from 3-chloro-2-methylpropionate (but not from 3-chloro*butyrate*). The reductive cyclization procedure applies neither to the phenylcyclopropane **11** nor to the (*tert*-butyldimethylsiloxy)cyclopropane **8**. These are in turn available by methylenation of ketene silyl acetals with the Furukawa reagent.[29] Other less cumbersome modifications of the Simmons–Smith conditions[30] did not work well. We note in passing that *the cyclopropanation reaction of silyl ketene acetals often results in the (partial) loss of the stereospecificity due to isomerization of the starting material under the reaction conditions.* This stands in contrast to the complete stereospecificity with enol silyl ethers of ketones and aldehydes.[31]

Stereoselective Preparation of γ-Lactones and Cyclopropanecarboxylates. The *tert*-butoxide-modified homoenolate adds to 2-phenylpropanal in a stereoselective manner producing **26** and **27** in a 6:1 ratio (Table VII, entry 1). In connection with projects to make use of such stereoselection for the elaboration of functionalized steroid side chains,[25] we extended efforts to examine the stereochemistry of the substitution reactions at the asymmetric center bearing the secondary alcohol. With the ecdysone-type problem in mind,[25] inversion of this chiral center was examined. The specific positioning of functional groups in **27** implied that an internal solvolysis reaction may alleviate the use of rather exotic reagents, (e.g., KO_2[32]) often required in a sterically conjested situation.[33] The major adduct **26** was mesylated (**28**), and the ester group was then hydrolyzed with aqueous KOH. During this latter reaction the resultant carboxylate anion effected displacement of the mesylate to give the lactone **30** in 74% yield after treatment with acid (Scheme IV). The same sequence was also performed on the minor adduct **27**. In both cases, the reaction was stereospecific.

The mesylates in Scheme V also serve nicely as precursors to cyclopropanecarboxylates (cf. a methylgorgosterol problem[25]). Thus, treatment of **28** with potassium *tert*-butoxide in THF gave **32** as a 86:14 mixture of isomers. The same procedure performed for **29** gave **33** as a 99:1 mixture of isomers, which were different from the isomers of 32 by capillary GLC analysis. This confirmed the stereospecificity of the inversion reaction. The trans stereochemistry was assigned to the major product on the basic of the literature precedents.[34]

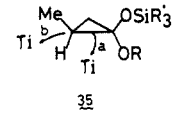
Scheme IV



Oxidation of the 4-hydroxy esters obtained in the present study could be achieved readily with standard chromium-based reagents, providing a ready access to synthetically useful 4-keto esters. Utilities of γ-lactones have been well-documented.[36]

Mechanistic Consideration. The experimental data presented above answer some mechanistic problems in the reaction of the siloxycyclopropanes with $TiCl_4$. As to the two possible mechanisms of the prototypical $TiCl_4$-mediated reaction of the cyclopropane **4** in Scheme I, the second path, i.e., the metal–homoenolate route, has been shown viable. The following pieces of evidence indicate that the contribution of path a is at best negligible. Recent comprehensive studies[15a] have revealed that the eq 3 type of reaction can be effected only by very special (Lewis acidic) catalysts (e.g., titanium and zinc salts), which generate nucleophilic homoenolates upon reaction with the siloxycyclopropane **4**. Other common Lewis acids fail to mediate the reaction, since they either do not form homoenolates (e.g., $AlCl_3$, $BF_3{\cdot}Et_2O$, Me_3SiOTf, Me_3SiI) or form unreactive homoenolates ($SnCl_4$, $TeCl_4$, $SbCl_5$).[15a]

The experimental results also shed light on the way in which $TiCl_4$ reacts with the cyclopropane. As depicted in Scheme VI, the initial interaction of the metal with the cyclopropane may occur either on the siloxy oxygen to form a titanium alkoxide (path a) or on the strained σ bond to form a cationic species such as **34** (path b). The formation of significant amounts of the silyl ester **9** and isopropyl chloride in the reaction of (*tert-butyldimethyl*siloxy)cyclopropane **8** (eq 5) is compatible only with path b. Loss of an alkyl group from a cationic species related to **34** has been noted previously.[37] When the silyl group (SiR'_3) is *trimethyl*silyl (e.g., **4**), loss of this group from **34** must be favored overwhelmingly over the cleavage of the OR bond. In addition, we have already shown that path a is a highly unlikely mechanism for the ring cleavage of **4** with various main group metals.[15a] The regiochemistry of the ring cleavage of cyclopropanols with electrophiles is known to be dependent on the ring substituents as well as the nature of the electrophile.[24] The regioselectivity observed for the siloxycyclopropanes **10** and **11** is similar to the one for substituted cyclopropanols with mercury salts, while the degree of selectivity is much lower.[24]

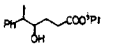
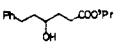
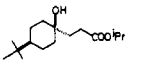


35

The ring cleavage of the chiral cyclopropane (*R*)-**10b** at the more substituted bond creates a new chiral center at the carbon

(29) (a) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1966**, 3353. (b) Cf.: Rousseaux, G.; Slowgui, N. *Ibid.* **1983**, *24*, 1251.
(30) Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React.* **1975**, *20*, 1.
(31) Cf.: Miyano, S.; Izumi, Y.; Fujii, H.; Hashimoto, H. *Synthesis* **1977**, 700. Conia, J. M.; Girard, C. *Tetrahedron Lett.* **1973**, 2767.
(32) San Fillippo, J., Jr.; Chern, C.-I.; Valentine, J. S. *J. Org. Chem.* **1975**, *40*, 1678. Corey, E. J.; Nicolaou, K. C.; Shibasaki, M.; Machida, Y.; Shiner, C. S. *Tetrahedron Lett.* **1975**, 3183.
(33) Cf.: Ishiguro, M.; Saito, H.; Sakamoto, A.; Ikekawa, N. *Chem. Pharm. Bull.* **1978**, *26*, 3715.
(34) Cf.: Sato, S.; Akaiwa, A.; Fujimoto, Y.; Ishiguro, J.; Ikekawa, N. *Chem. Pharm. Bull.* **1981**, *29*, 406.
(35) Walkup, R. D.; Anderson, C. D.; Djerassi, C. *Tetrahedron Lett.* **1979**, 767.
(36) Eschenmoser, A.; Felix, D.; Ohloff, G. *Helv. Chim. Acta* **1967**, *50*, 708. Fehr, C.; Ohloff, G. *Ibid.* **1979**, *62*, 2655. Jacobson, R. M.; Clader, J. W. *Tetrahedron Lett.* **1980**, *21*, 1205.
(37) Danishefsky, S.; Vaughan, K.; Gadwood, R.; Tsuzuki, K. *J. Am. Chem. Soc.* **1981**, *103*, 4136.

Table VI. The Reaction of the *tert*-Butoxide-Modified Homoenolate (eq 11)[a]

entry	carbonyl compds	condns temp (°C), time (h)	product	% yield
1	2-phenylpropanal	−20, 3		81[b] (86:14)[c]
2	3-phenylpropanal	25, 1.5		86
3	acetophenone	20, 1		93
4	3-pentanone	20, 18		82
5	5-nonanone	20, 18		84
6	benzophenone	ca. 20, 40		49[b,e,f]
7	cyclopentanone	20, 2		74
8	cyclohexanone	20, 1		91
9	2-methylcyclohexanone	ca. 20, 25		81 (84:16)[d]
10	3-methylcyclohexanone	ca. 20, 1		91 (88:12)[d]
11	4-*tert*-butylcyclohexanone	20, 1.5		94 (88:12)[d]
12	4-*tert*-butylcyclohexanone	−20, 3		50[b,e] (91:9)[d,f]

[a] The reaction was run till the disappearance of the starting material (except entry 2 where the reaction was instantaneous). The product was isolated as a γ-lactone except those indicated. [b] The adduct was isolated as a 4-hydroxy ester. [c] The ratio between **26** and **27**. [d] The ratio of the equatorially attacked product vs. the axially attacked one. [e] The reaction was not complete. [f] The product analysis was performed after lactonization (TsOH).

Table VII. Stereoselectivity

entry	R-Met	with cyclohexanones % equatorial 4-*t*-Bu	2-Me	3-Me	2-phenylpropanal % Cram	**25** % chelate prod[b]	ref
1	**5a** + $Ti(O\text{-}t\text{-}Bu)_4$	91[a]	84[a]	86[a]	86[a]		
2	**5a,b**				85	79[b]	
3	Me_2TiCl_2	82	94		80		25
4	$MeTi(O\text{-}i\text{-}Pr)_3$	94	94	89	88		25
5	$LiCH_2CH_2COOLi$	ca. 78					9
6	MeLi	65	88		66		28a,b
7	$PhCH_2CH_2MgBr$	73	97	87			28c

[a] Stereochemical assignment was based on the assumption that the homoenolate behaves essentially like simple titanium alkyl. [b] The Percentage of the product formation (eq 12) due to presumed chelate formation (ref 28b).

attached to the metal in **13** (Scheme III). The chirality of this center would be controlled primarily by the mode of the initial C–C bond cleavages, i.e., retention (**35**, a) of inversion (b). Because direct determination of the chirality in **13** was not possible, we have conducted an experiment (eq 7) which would indirectly elucidate the stereochemistry in **13**. The result unfortunately was inconclusive since the β-methyl product obtained in eq 7 was racemic. The formation of the optically active α-methyl isomers **14** and **15** confirms that the cyclopropane (*R*)-**10b** itself had not racemized before the reaction with $TiCl_4$, and the stereochemical factors involved in the following three stages must have been responsible for the formation of the racemates: (1) the initial ring cleavage, (2) the configurational stability of the C–Ti bond in **13**, and (3) the final electrophilic rapture of the Ti–C bond in **13**. Literature precedents[38] suggest that the last factor is the last likely reason of the racemization, since such reactions generally proceed with retention of the configuration. If the formation of the racemates were due to the initial ring cleavage, the titanium atom must have cleaved the ring with both retention and inversion in exactly the same rate. Finally, there is currently no information available for the configurational stability of the (elusive) secondary alkyl titanium species.[26] Many of the anionic species are known to have marginal configurational stability,[39] and it is possible that the homoenolate **13**, desite the internal chelation, racemizes quickly before being captured by the electrophile. It is clear that we need more of the basic information in order to clarify these mechanistic ambiguities.

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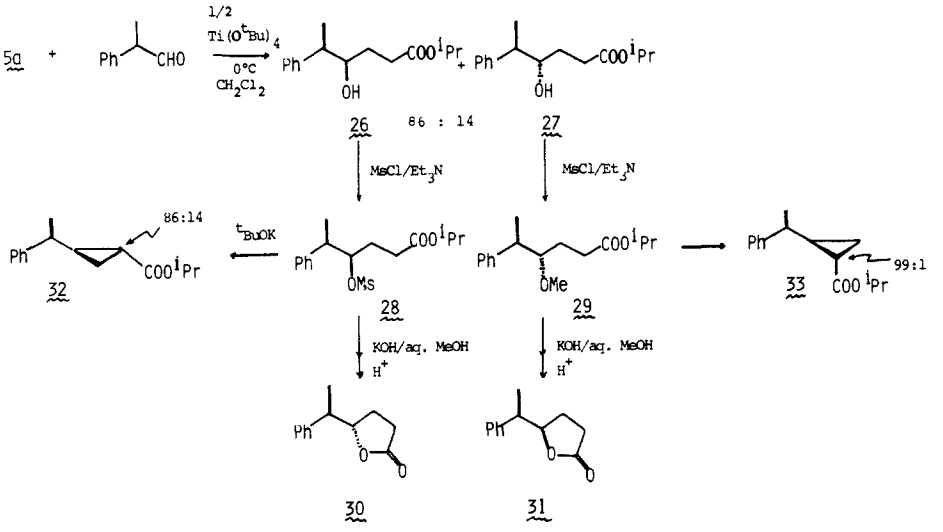
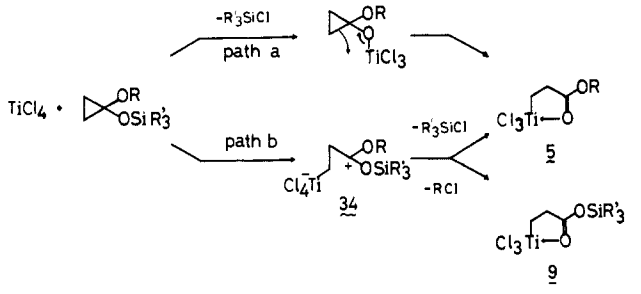
Scheme V



Scheme VI



Experimental Section

1-Alkoxy-1-(trimethylsiloxy)cyclopropane (4). 1-Ethoxy compound **4b** was prepared as reported by Ruhlmann.[4] 1-Isopropoxy compound **4a** was prepared in the same manner (54%): bp 107–115 °C (100 mmHg); IR (neat) 2935 (m), 1446 (m), 1298 (s), 1250 (s), 1225 (s), 1118 (m), 1016 (s), 985 (s), 870 (s), 845 cm^{-1} (s); ^1H NMR (CCl_4) δ 0.08 (s, 9 H), 0.55–0.80 (symmetrical m, 4 H), 1.07 (d, 6 H, J = 6 Hz), 3.91 (qq, 1 H, J = 6 Hz.

Anal. $C_9H_{20}O_2Si$: C, H.

2-Isopropoxy-1-methyl-1-(trimethylsiloxy)cyclopropane (10a) was prepared as **4** in 61% yield (92% pure by GLC) with an isomeric ratio of 42:58: bp 103–106 °C (90 mmHg): ^1H NMR (CCl_4) δ 0.11 (s, 5.2 H), 0.16 (s, 3.8 H), 0.75–1.25 (m, 12 H), 3.92 (qq, J = 6, 6 Hz).

2-Methoxy-1-methyl-1-(trimethylsiloxy)cyclopropane (10b) was prepared as **4** in 60% yield from methyl 3-chloro-2-methylpropionate in an isomeric ratio of 49:51: ^1H NMR (CCl_4) δ 0.11 (s, 4.4 H), 0.16 (s, 4.6 H), 0.7–1.2 (m, 6 H), 3.23 (s, 1.4 H), 3.30 (s, 1.6 H); MS, *m/e* 174 (M^+), 159, 146, 105, 90, 75, 73.

1-(*tert*-Butyldimethylsiloxy)-1-isopropoxycyclopropane (8). To a solution of diisopropylamine (1.45 g, 14.3 mmol) in 20 mL of THF at −40 °C was added 1.71 M butyllithium in hexane (8.5 mL, 14.5 mmol). After 30 min, the temperature was lowered to −78 °C, and isopropyl acetate (1.13 mg, 11.1 mmol) was added dropwise to the solution. After the mixture was stirred for 5 min, *tert*-butyldimethylsilyl chloride (2.19 g, 14.6 mmol) in 5.15 g of HMPA (28 mmol) was added. The mixture was stirred for 5 min, gradually allowed to warm to room temperature during 30 min, and diluted with 20 mL of hexane. The organic layer was washed five times with water and once with saturated NaCl, dried, and concentrated. The crude product was dissolved in 30 mL of ether, diethyl zinc (2.56 g, 20.7 mmol) was added, and then diiodomethane (5.65 g, 21.1 mmol) was added over 5 min. After 1 h, dry hexane (30 mL) was added, and gaseous NH_3 was introduced at 0 °C. Chromatographic purification of the crude product obtained after filtration and concentration gave 1.56 g (61%) of the title cyclopropane: bp 57–58 °C (6 mmHg); IR (neat) 1450 (m), 1300 (m), 1220 (m), 1118 (m), 1018 (m), 980 (s), 852 (m), 838 (s), 778 cm^{-1} (s); ^1H NMR (CCl_4) δ 0.13 (s, 6 H), 0.65–1.00 (m, 13 H, involving s at 1.00), 1.10 (d, J = 6 Hz, 6 H), 3.88 (qq, J = 6 Hz, 1 H).

Anal. $C_{12}H_{26}O_2Si$: C, H.

2-Phenyl-1-ethoxy-1-(trimethylsiloxy)cyclopropane (11) was prepared by methylenation of the corresponding ketene acetal as above. The material after MPLC purification (ethyl acetate in hexane) still contained impurities and was used as such. Bp 70–72 °C (0.12 mmHg); IR 1600 (w), 1495 (m), 1455 (m), 1430 (m), 1365 (m), 1280 (s), 1250 (s), 1215 (s), 1195 (s), 1108 (m), 1055 (s), 980 (s), 880 (s), 820 cm^{-1} (s); MS, *m/e* (rel intensity) 250 (M^+, 78), 235 (15), 205 (72), 191 (20), 176 (66), 132 (98), 119 (50), 131 (90), 117 (80), 104 (95), 75 (95), 73 (95). Both stereoisomers showed virtually identical mass spectra.

Isopropyl 3-(Trichlorotitanio)propionate (5a). To a water-cooled solution of $TiCl_4$ (110 micro l, 1.0 mmol) in 2.0 mL of hexane was added the cyclopropane **4a** (220 mL, 1.0 mmol) at 21 °C over 20 s. The initially formed white milky mixture turned brown in 10 s, and finally deep purple colored microcrystals fell out. Heat evolution continued for a few minutes. The mixture was let stand for 30 min; NMR analysis of the supernatant revealed the absence of **5a** and the quantitative formation of chlorotrimethylsilane (with 1,1,2,2-tetrachloroethane as an internal standard). The supernatant was removed by a syringe and the crystals were washed three times with hexane. Th ehomoenolate **5a** weighed 223 mg (83%). This procedure could be scaled up to a 10-g scale without modification. An experiment performed in $CDCl_3$ at room temperature produced the homoenolate in 89% NMR yield. Recrystallization from methylene chloride/hexane gave an analytical sample as deep purple thin needles. The titanium alkyl melts at 90–95 °C with color change to reddish brown and sublimes with some decomposition at 90–110 °C (0.005 (mmHg)). For the IR and NMR spectra, Tables I and II: resonance Raman (514.5 nm, solid) 360 (s), 285 (sh), 280 (br s), 265 (br s), 120 (m). Anal. Calcd for $C_6H_{11}O_2Cl_3Ti$: C, 26.75; H, 4.12. Found: C, 26.59; H, 4.22.

Ethyl (**5b**) and methyl ester complex (**5c**) were prepared in a similar manner, and spectra are given in Tables I and II.

The Reaction of the Titanium Homoenolate with Oxidizing Agents. (a) With Bromine. The homoenolate **5a** prepared from 1.0 mmol each of $TiCl_4$ and **4a** in CCl_4 at room temperature was treated with 1.0 mL of 1.0 M bromine solution in CCl_4 at 0 °C. Aqueous work involving treatment with a hypo solution gave 150 mg of isopropyl 3-bromopropionate (83% based on **4a**) identical with an authentic sample by NMR. The titanium alkyl was inert to NBS.

(b) With Molecular Oxygen. The titanium alkyl prepared on a 0.02-mmol scale in CCl_4 was stirred under oxygen for 5 min. Aqueous workup gave 18 mg (68% from **4a**) of isopropyl 3-hydroxypropanoate: IR (neat) 3450 (br), 1733 cm^{-1} (s); ^1H NMR (CCl_4) 1.23 (d, 6 H, J = 6 Hz), 2.40 (t, 2 H, J = 6 Hz), 3.70 (t, 2 H, J = 6 Hz), 4.95 (qq, 1 H, J = 6 Hz); MS, *m/e* 132 (M^+).

The Reaction of the Titanium Homoenolate with $NbCl_5$. To a suspension of $NbCl_5$ (85 mg, 0.315 mmol) in 0.25 mL of $CDCl_3$ was added at 0 °C a solution of **5b** (ca. 0.31 mmol) in 0.3 mL of the same solvent. ^1H NMR analysis of the resultant homogeneous deep red solution after 7 min indicated quantitative transmetalation reaction: ^1H NMR ($CDCl_3$) δ 1.50 (t, J = 7 Hz), 3.3–3.9 (m, 4 H, involving t-like peak at 3.74, J = ca. 7 Hz), 4.65 (q, J = 7 Hz).

The Reaction of the Titanium Homoenolate with $SnCl_4$. To a CCl_4 solution of **5b** prepared from 0.20 mmol each of reactants was added $SnCl_4$ (23 mL, 0.20 mmol) at 26 °C, and the red color of the titanium compound faded rapidly. NMR analysis indicated quantitative formation of the corresponding tin homoenolate, which was isolated by distillation and shown to be identical with an authentic sample.[15a]

The Reaction of the Trichlorotitanium Homoenolate (5) with Alde-

hydes. (A) With Preformed 5. The homoenolate prepared as above (ca. 1.5 mmol) was dissolved in 2 mL of methylene chloride at 0 °C and an aldehyde (1.0 mmol) in 1 mL of methylene chloride was added. After a period indicated in Table III (see Table I in supplementary material for details), the reaction mixture was poured into water and extracted with ether. The ethereal extract was washed with water, aqueous $NaHCO_3$, and saturated NaCl, dried over $MgSO_4$, and concentrated. Purification of the crude product either by distillation or column chromatography gave the expected adduct.

The 4-hydroxy ester, particularly ethyl esters, is highly susceptible to lactonization, and the addition product was obtained mainly as a lactone if the reaction was quenched by addition of water into the reaction mixture. In such an event, the crude product was treated with *p*-toluenesulfonic acid in benzene to complete the lactone formation.

(B) With 5 Generated in Situ. To a mixture of an aldehyde (1 mmol) and $TiCl_4$ (1.1 mmol) in 3 mL of methylene chloride at 0 °C was added the cyclopropane (1.3 mmol), and the mixture was stirred for about 1 h. The mixture was worked up as above.

Isopropyl 3-(Trichlorotitanio)-2-methylpropionate (12a). To a solution of $TiCl_4$ (0.11 mL, 1.0 mmol) in 1.5 mL of hexane was added **10a** (92% pure, 258 μL, 1.00 mmol) at room temperature over 1 min. The mixture was stirred for 30 min, and the precipitated crystals were washed three times with a small amount of hexane to give a spectroscopically pure homoenolate (155 mg, 55%): IR, see Table II; ^1H NMR ($CDCl_3$) δ 1.25 (d, 3 H, J = 7 Hz), 1.51 (d, 6 H, J = 6 Hz), 2.42 (dd, 1 H, J = 6, 12.5 Hz, CHTi), 3.05 (dd, 1 H, J = 7.5, 12.5 Hz, CHTi), 3.48 (ddq, J = 6, 7.5, 7, CHCO), 5.45 (qq, J = 6 Hz).

Alternatively, the reaction was performed in CCl_4 at 21 °C; an exothermic reaction occurred and was complete after 3 min by NMR (45% yield). After 2 min, 1.00 mmol of bromine in CCl_4 was added at 0 °C over 30 s. Ether and water were added and the organic layer was washed with water, aqueous sodium thiosulfate, aqueous NaHCO3, and saturated NaCl. The crude mixture was analyzed by ^1H NMR to reveal the formation of isopropyl 3-bromo-2-methylpropionate (100% based on the titanium homoenolate) and the absence of isopropyl 3-bromobutanoate.

To a solution of a 155-mg portion of the crystals in 0.5 mL of methylene chloride was added 3-phenylpropanal (47 mg, 0.35 mmol) at 0 °C. The mixture was stirred for 3 h at 29 °C, quenched with water, and extracted with ether. After the mixture was dried and concentrated, 68 mg of 4-hydroxy-2-methyl-6-phenylhexanoic lactone (95%) homogeneous by TLC was obtained.

The Reaction of 10b and 3-Phenylpropanal. To a dark red solution of a mixture of $TiCl_4$ (0.1 mL, 1.0 mmol) and the aldehyde (132 μL, 1.00 mL) in 1 mL of methylene chloride at 0 °C was added the cyclopropane (neat, 243 μL, 1.20 mmol). The resulting dark solution was stirred for 1.5 h, at which point still some aldehyde remains. An additional 40 μL of **10b** (0.2 mmol) was added and the mixture was stirred for 1 h. Water (0.5 mL) and ether (2 mL) were added, and the organic layer was separated. The crude product (202 mg) consisted of four major components (TLC) with two IR bands at 1776 and 1731 cm^{-1}. This oil was heated with 10 mg of TsOH in refluxing benzene for 30 min, affording 178 mg of an oily product, now devoid of the most polar spot of the four, as well as the 1731-cm^{-1} IR band.

Purification of the crude product on MPLC (Lobar, Grosse A; 15% ethyl acetate in hexane) gave five fractions.

Structural assignment could not be made for the first and the second fraction.

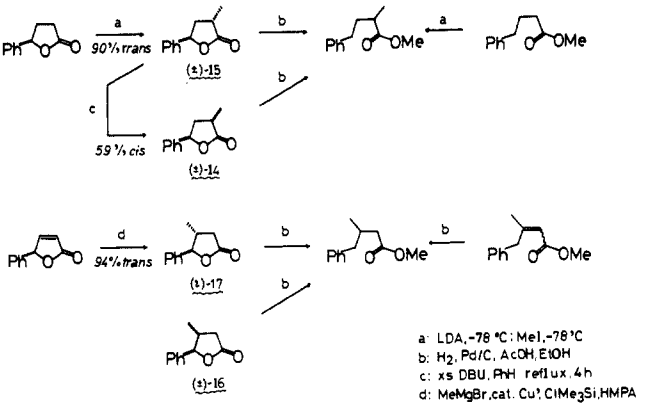
The third fraction (85 mg) was 4-hydroxy-2-methyl-6-phenylhexanoic lactone (42% yield) as a 1:1 mixture of C-2 epimers as indicated by ^{13}C NMR: IR (CCl_4) 1769 cm^{-1} (s); ^1H NMR (CCl_4) δ 1.19 (d, superimposed on a multiplet, br s on irradiation at 2.43, 3 H, J = 7 Hz, CH_3CH), 1.7–2.9 (m, 7 H, CH_2, CH), 3.9–4.5 (m, remains unchanged on irradiation at 2.43, 1 H, CHO), 7.08 (s, 5 H, C_6H_5).

Trans isomer prepared by kinetic methylation of the unsubstituted lactone: IR (neat) 1760; ^1H NMR (CCl_4) 1.20 (d, 3 H, J = 7 Hz), 1.8–2.9 (m, 7 H), 4.31 cm^{-1} (unresolved quintet, 1 H, J = ca. 7 Hz); ^{13}C NMR ($CDCl_3$) δ 179.8, 140.7, 128.4, 126.1, 77.3, 37.2, 35.5, 34.0, 31.7, 15.9: MS, m/e (rel intensity) 204 (M^+, 31), 131 (50), 130 (100), 112 (15), 92 (63), 91 (81).

Cis isomer prepared by epimerization of the trans isomer by kinetic protonation of the enolate: ^1H NMR (CCl_4) δ 1.21 (d, J = 7 Hz), 1.5–2.9 (m), 3.85–4.45 (m centered at 4.20, 1 H), 7.10 (s, 5 H); ^{13}C NMR ($CDCl_3$) δ 179.3, 140.8, 126.1, 128.4, 77.5, 37.3, 35.9, 31.7, 15.1; MS, m/e (rel intensity) 204 (M^+, 20), 131 (45), 130 (100), 92 (25), 91 (10).

The fourth fraction (36 mg) was one isomer of 4-hydroxy-3-methyl-6-phenylhexanoic lactone (18%): IR (CCl_4) 1776 cm^{-1} (s); ^1H NMR (CCl_4) δ 1.07 (br d, br s on irradiation at 2.23, 3 H, CH_3), 1.6–2.9 (m, 7 H, CH_2, CH), 3.84 (br dt, br t on irradiation at 2.23, J = 6, 6 Hz, 1 H, CHO), 7.09 (s, 5 H, C_6H_5); MS, m/e (rel intensity) 204 (M^+, 40), 144 (100), 117 (80), 104 (60), 92 (78), 91 (100).

Scheme VII



The fifth fraction (18 mg) was the other isomer of **17** (9%): IR (CCl_4) 1774 cm^{-1}; ^1H NMR (CCl_4) δ 1.01 (d, br s on irradiation at 2.35, J = 7 Hz, CH_3), 1.5–2.95 (m, 7 H, CH_2, CH), 4.25 (dt, unresolved t, J = 5, 8 Hz, CHO); MS, m/e (rel intensity) 204 (M^+, 38), 144 (80), 107 (65), 104 (60), 92 (95), 91 (100).

The fractions 3–5 were separable by capillary GLC (OV-101, 20 m, 180 °C).

The Reaction of (2*R*)-1-(Trimethylsiloxy)-1-methoxy-2-cyclopropane (*R*-10b) with Benzaldehyde. To a solution of $TiCl_4$ (66 μL, 0.6 mmol) in 1 mL of methylene chloride was added benzaldehyde (51 μL, 0.50 mmol) at 0 °C. To this yellow suspension was added the cyclopropane (142 μL, 0.70 mmol), and the resulting dark reddish mixture was stirred for 15 min at 0 °C. The mixture was diluted with ether and washed three times with water (0.7 mL × 3). Ether was removed in vacuo, and then the residual oil was treated with 0.1 g of KOH in aqueous MeOH at 50 °C for 1 h. The mixture was concentrated in vacuo, and the residue was washed twice with ether and evacuated in vacuo. 2-Chloropyridine methiodide (0.2 g), triethylamine (0.3 mL), and 1 mL of dry THF were added and the mixture was refluxed for 1 h. After dilution with 4 mL of hexane, the supernatant was filtered, and the filtrate was concentrated. Capillary GLC analysis of the crude lactone (PEG-20M, 0.25 mm × 20 m, 170 °C) indicated three peaks, corresponding to the *trans*-α-methyl isomer (**15**), a mixture of *cis*-α-methyl (**14**) and *trans*-β-methyl isomers (**17**), and *cis*-β-methyl isomer (**16**) in a ratio of 34:37:29 (retention times, 20.2, 22.4, and 23.3 min, respectively). These data combined with the 200-MHz ^1H NMR signals due to the clearly discernible methyl and CH–O protons indicated the *cis*- and *trans*-α-methyl and *cis*- and *trans*-β-methyl isomers were formed in a ratio of 29:32:28:11 (in 50% isolated yield, 44 mg).

***cis*-α-Methyl isomer (14)**: IR (neat) 1770, 1.31 (d, J = 7.2 Hz), 2.2–2.5 (m), 2.6–2.9 (m), 5.34 (dd, J = 5.7, 10.6 Hz), 7.36 cm^{-1} (s).

***trans*-α-Methyl isomer (15)**: IR (neat) 1770 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.31 (d, J = 7.2 Hz), 2.2–2.5 (m), 2.71 (sextet, J = 7 Hz), 5.56 (dd, J = 5.0, 7.0 Hz), 7.33 (m).

***cis*-β-Methyl isomer (16)**: IR (neat) 1770 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.69 (d, J = 6.9 Hz), 2.2–2.4 (m), 2.7–2.9 (m), 5.59 (d, J = 5.9 Hz), 7.35 (m).

***trans*-β-Methyl isomer (17)**: IR (neat) 1770 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.20 (d, J = 6.3 Hz), 2.2–2.6 (m), 2.79 (dd, J = 7.2, 16.0 Hz), 4.94 (d, 8.0 Hz), 7.37 (m); MS, m/e (rel intensity) 176 (M^+, 40), 107 (100), 105 (82), 77 (31), 42 (54).

These isomers were correlated to authentic racemic samples as indicated in Scheme VII.

These isomers were examined for their optical purity with the aid of tris[3-(heptafluoropropylhydroxymethylene)-*d*-caphorato]europium(III) in $CDCl_3$. Signals due to the CH–O proton in both of the β-methyl isomers **16** and **17** readily separated into doublets of *equal* intensity, indicating complete racemization. The *cis*-α-methyl isomer (**14**) did not show any trace of the antipode. The *trans*-α-methyl isomer (**15**) was at least 70% optically active, as indicated by the well-separated pairs of the methyl doublets.

The Reaction of the Homoenolate Treated with Lithium Methoxide. To a weighed amount of lithium methoxide placed in a flask was added a solution of **5b**. An exothermic reaction ensued and the mixture was stirred for 30 min. Benzaldehyde was added at 0 °C and stirred for 1 h. Aqueous workup afforded the pinacol **21**, which was identical with an authentic sample.[27]

The Reaction of the Alkoxide-Modified Homoenolate. The purified homoenolate **5b** (1.5 mmol) was dissolved in 3 mL of methylene chloride at 0 °C and $Ti(OR)_4$ (0.75 mmol) was added. After 5 min, 1 mmol of

a carbonyl compound was added. The mixture was stirred for a period indicated in Tables V and VI (see Tables II and III in supplementary material for details). The mixture was poured into a stirred mixture of ether and water. After 10 min, the ethereal layer was separated and the aqueous layer was extracted 3 times with ether. The combined extract was washed with water, aqueous $NaHCO_3$, and saturated NaCl. After the mixture was dried and concentrated, the product was purified to obtain the desired 4-hydroxy ester or lactone. For unreactive substrate, 2 equiv of **5a** and 1 equiv of $Ti(OR)_4$ was used. The physical properties of the products in these tables are in the supplementary material.

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Supplementary Material Available: General data of experiments, tabular presentation of the experimental details of the homoenolate additions, and physical properties of the 4-hydroxy esters and the lactones obtained by these additions, including those shown in Scheme V (13 pages). Ordering information is given on any current masthead page.

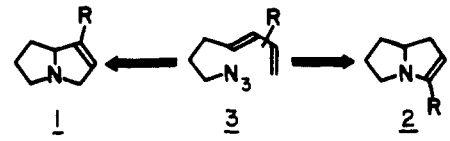
Topological Selectivity in the Intramolecular [4 + 1] Pyrroline Annulation. Formal Total Stereospecific Synthesis of (±)-Supinidine, (±)-Isoretronecanol, and (±)-Trachelanthamidine

Tomas Hudlicky,*[1] James O. Frazier, Gustavo Seoane, Mark Tiedje, Ana Seoane, Lawrence D. Kwart, and Chris Beal

Contribution from the Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061. *Received November 22, 1985*

Abstract: The preparation and cycloadditions of azidodienes **13** and **14** are described in detail. The synthesis of pyrrolines **1** and **2** is reported, and the conditions are revealed to achieve maximum selectivity in their preparation. The topography of the ultimately prepared pyrrolines depends primarily on the substitution parameters of the starting dienes and on the conditions of rearrangement of their respective vinylaziridines **15** and **16**. The former parameter is easily controlled through the vinylogous Reformatsky reaction of ethyl 4-bromocrotonate with aldehyde precursors. The latter parameter depends on the choice of thermolytic vs. nucleophilic activation of particular bonds in vinylaziridines **15** and **16**. The flexibility and practicality of this method is exemplified by several convergent approaches to substituted pyrrolines **1** and **2** and their conversion to the title pyrrolizidine alkaloids. Stereospecific preparation of saturated pyrrolizidines **35** is also described. A detailed study of the base-catalyzed elimination of β-acetoxy esters was performed, and the stereochemical consequences are reported for the formation of *E* and *Z* geometric isomers of dienes **13**.

Several years ago we implemented a strategy directed toward a system-oriented design of cyclopentanoid terpenes.[2] The key element of this strategy featured a formal [4 + 1] addition of a carbenoid across an appropriately functionalized conjugated diene. In the context of alkaloid synthesis, we have pursued a similar thought in the logical extrapolation of the above principles to the additions of electron-deficient nitrogen species to conjugated dienes. Preliminary results bode well for the synthesis of regioisomeric pyrrolizidines **1** and **2** by the internal cycloaddition of dienic azides **3**, where the topography of the pyrrolines would be controlled either by the position of the substituent in **3** or by experimental conditions through a differential activation of specific vinylaziridine bonds toward ring opening and subsequent formation of the fused pyrrolines (eq 1).[3]



1 3 2 (1)

R = H, alkyl, CO_2R'

It appeared that such a method would find wide applicability in the synthesis of fused pyrrolines, particularly the pyrrolizidine alkaloids, which are ubiquitous throughout the plant and animal kingdom and which are endowed with a vast array of biological properties.[4] The unsaturated ester site provides an opportunity

(1) Fellow of the Alfred P. Sloan Foundation, 1981-1985; Recipient of the National Institutes of Health Research Career Development Award, 1984-1989 (AI-00564).

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