Some Deoxygenation Reactions with Low-Valent Titanium (TiCl₃/LiAlH₄)

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A low-valent titanium reagent prepared by treating anhydrous $TiCl_3$ with 0.25 molar equiv of $LiAlH_4$ is capable of carrying out reductions on numerous types of organic systems: epoxides are deoxygenated nonstereospecifically to olefins (nine examples); bromohydrins are reduced nonstereospecifically to olefins (seven examples); allylic and benzylic alcohols are reductively coupled to hydrocarbons, although intramolecular coupling is not possible; certain α-hydroxy ketones are deoxygenated to ketones; and cyanohydrins are deoxygenated in low yield to nitriles. Mechanisms are proposed to account for the observed results.

Several years ago, we observed[1] that ketones could be deoxygenatively dimerized to olefins on treatment with a reagent prepared by reacting a tetrahydrofuran (THF) solution of anhydrous $TiCl_3$ with 0.5 molar equiv of $LiAlH_4$. Subsequent to our initial disclosure, however, we found the ketone coupling reaction to give variable results depending on the exact batches of reagents used. After considerable experimentation, we developed an improved carbonyl coupling procedure based on the use of highly active titanium metal,[2] and we did not further pursue the use of $LiAlH_4/TiCl_3$ for carbonyl coupling. We did, however, find that the $LiAlH_4/TiCl_3$ reagent effects a variety of other organic reductions reproducibly and in good yield. Our investigations of these reductions form the basis of this paper.

Reduction of Epoxides. The deoxygenation of epoxides to olefins is a transformation which can be effected by numerous reagents, including strongly reducing metals or metal salts such as chromium atoms,[3] zinc,[4] magnesium amalgam,[5] zinc–copper couple,[6] chromous ion,[7] low-valent tungsten complexes,[8] and $FeCl_3$-BuLi.[9] We have found that $TiCl_3/LiAlH_4$ is also capable of carrying out this reaction.[10] Operating on the assumption that a Ti(II) species is the active reducing agent formed on reduction of $TiCl_3$, we carried out our reactions using the exact molar ratio of $TiCl_3/LiAlH_4$ necessary for stoichiometric formation of Ti(II), i.e., 4:1. Optimum reaction conditions were established in a study of the reduction of 1,2-epoxydecane (Table I). We found that heating of the reaction is required and that a 4:1:2 ratio of $TiCl_3/LiAlH_4$/epoxide is necessary.

Our results on the reduction of some representative epoxides are given in Table II.

With the exceptions of α-methylstyrene oxide and α-pinene oxide, these deoxygenations take place cleanly and in acceptable yields. We suspect that the two epoxides which reduce poorly suffer competing side reactions from carbonium ion rearrangements since both would be expected to be highly acid sensitive.

The mechanism of this reduction is probably similar to that postulated by Kochi for the related chromous ion reduction.[7]
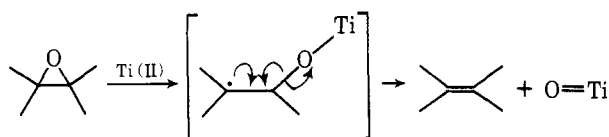
This mechanism, in which stepwise deoxygenation through an intermediate radical occurs, would explain the lack of stereospecificity observed in the *cis*- and *trans*-5-decene epoxide reductions.

If this mechanism is correct, it suggests that low-valent titanium-induced deoxygenation should be a general reaction for structures of type A → B where the group X neighboring
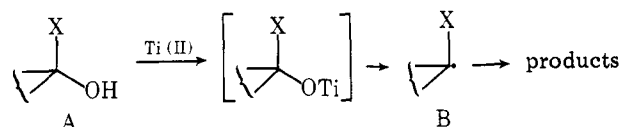

the oxygen can either stabilize a radical center or undergo further reaction.

For example, if in structure A the group X = C–Br, then deoxygenated radical intermediate B can lose Br by a low energy pathway. Thus, we predict that bromohydrins should reduce to give olefins. Similarly, if X = CN, deoxygenation of cyanohydrins to nitriles might occur [one would expect B (X = CN) to add a further electron to give a nitrile anion]. Similarly also, α-hydroxy ketones should reduce to ketones and allylic and benzylic alcohols should deoxygenate. All of these possibilities have been realized, and we now discuss them.

Reduction of Bromohydrins. There have been relatively few direct methods reported for reducing bromohydrins to olefins. As shown in Table III, however, the $TiCl_3/LiAlH_4$ reagent is most effective for this reduction.[11]

Synthetically, this reaction has several things to recommend it. All substrates tried reduce in good yield, and the conditions are nonacidic in contrast to the normal zinc–acetic acid method.[12] The reduction, however, is not stereospecific as shown from reactions of *threo*- and *erythro*-5-decene bromohydrins. In this respect, the results are similar to those obtained both with zinc[12] and with chromous ion.[13]

Table I. Deoxygenation of 1,2-Epoxydecane with TiCl₃/LiAlH₄

$$CH_3(CH_2)_7\overset{O}{\overset{\triangle}{CHCH_2}} \xrightarrow[\text{THF}]{\text{TiCl}_3/\text{LiAlH}_4} CH_3(CH_2)_7CH\!=\!CH_2$$
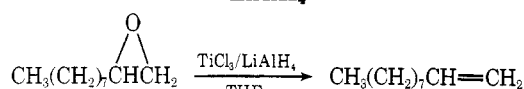
Trial	Rxn time, h	Rxn temperature, °C	Reagent ratio[a]	Yield,[b] %
1	4	20	4:1:2	Low
2	16	20	4:1:2	21
3	3	65	4:1:2	68
4	17	65	4:1:2	65
5	16	65	4:1:4	38

[a] The ratio represents molar equivalents of TiCl₃/LiAlH₄/epoxide. [b] Yield determined by GLC with an internal standard.

Table II. Deoxygenation of Some Epoxides with TiCl₃/LiAlH₄

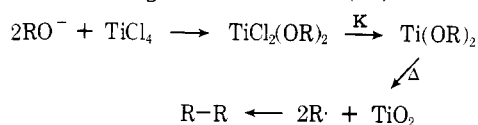$$\xrightarrow[\text{THF}]{\text{TiCl}_3/\text{LiAlH}_4{}^a}$$
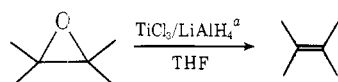
Reactant	Registry no.	Product	Yield,[b] %
Cyclohexene oxide	286-20-4	Cyclohexene	69
Cyclooctene oxide	286-62-4	Cyclooctene	53
α-Methylstyrene oxide	2085-88-3	α-Methylstyrene	36
5α,6α-Epoxycholestan-3β-ol	1250-95-9	Cholesterol	79
1,2-Epoxydecane	2404-44-6	1-Decene	67
1,2-Epoxydodecane	2855-19-8	1-Dodecene	68
α-Pinene oxide	1686-14-2	α-Pinene	11
cis-5,6-Epoxydecane	36229-64-8	5-Decene (21:79 cis/trans)[c]	70
trans-5,6-Epoxydecane	2165-61-9	5-Decene (18:82 cis/trans)[c]	70

[a] A molar ratio of 4:1:2 TiCl₃/LiAlH₄/epoxide was used. [b] With the exception of cholesterol, yields were determined by GLC using an internal standard. [c] Registry no.: cis-5-decene, 7433-78-5; trans-5-decene, 7433-56-9.

Mechanistically, we view the process as occurring by a pathway analogous to that proposed for the related chromous ion reduction in which an intermediate radical species is produced. An alternative concerted path is ruled out by the lack of stereospecificity observed in the reactions of the 5-decene bromohydrins.
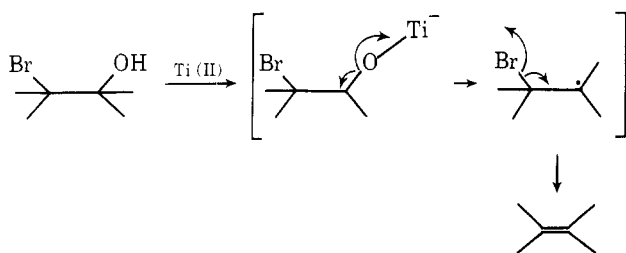
Coupling of Allylic and Benzylic Alcohols.
The titanium-induced coupling of allylic and benzylic alcohols was first observed by van Tamelen and Schwartz in 1965.[14] These workers found that when 2 equiv of alkoxide was added to TiCl₄ and the resulting dichlorotitanium(IV) dialkoxide was

$$2RO^- + TiCl_4 \longrightarrow TiCl_2(OR)_2 \xrightarrow{K} Ti(OR)_2$$
$$\downarrow \triangle$$
$$R\text{--}R \longleftarrow 2R\cdot + TiO_2$$

Table III. Reductions of Bromohydrins with TiCl₃/LiAlH₄

Substrate	Registry no.	Product	Yield, %
	1502-14-3	Cyclooctene	96
	56804-70-7	Indene	93
	1857-83-6	Cholesterol	79
2-Bromo-1-decanol	39579-74-3	1-Decene	74
2-Bromo-1-dodecanol	56804-71-8	1-Dodecene	91
erythro-5-Bromo-6-decanol	56804-72-9	5-Decene (80:20 trans/cis)	91
threo-5-Bromo-6-decanol	56804-73-0	5-Decene (70:30 trans/cis)	82

Table IV. Reductive Coupling of Alcohols with TiCl₃/LiAlH₄

Alcohol	Registry no.	Product	Yield, %
n-Decanol		No reaction	
Cholesterol		No reaction	
PhCH₂OH	100-51-6	PhCH₂CH₂Ph	78
PhCH(OH)CH₃	98-85-1	PhCH(CH₃)CH(CH₃)Ph	68
PhC(OH)(CH₃)₂	617-94-7	PhC(CH₃)₂C(CH₃)₂Ph	95
	4096-38-2		87
	4602-84-0		33

reduced with molten potassium in refluxing benzene, coupling to dimeric hydrocarbon was observed. Benzyl alcohol, for example, coupled to bibenzyl in 51% yield.

Subsequently, a modification based on the use of TiCl₃ and CH₃Li was introduced, simplifying the procedure.[15] We have

Scheme I

Table V. Attempted Intramolecular Diol Coupling with TiCl$_3$/LiAlH$_4$

Diol	Product	Yield, %
10	+ isomers	80
13	+ isomers	100
14	No reaction	
15	No reaction	
16		

Scheme II
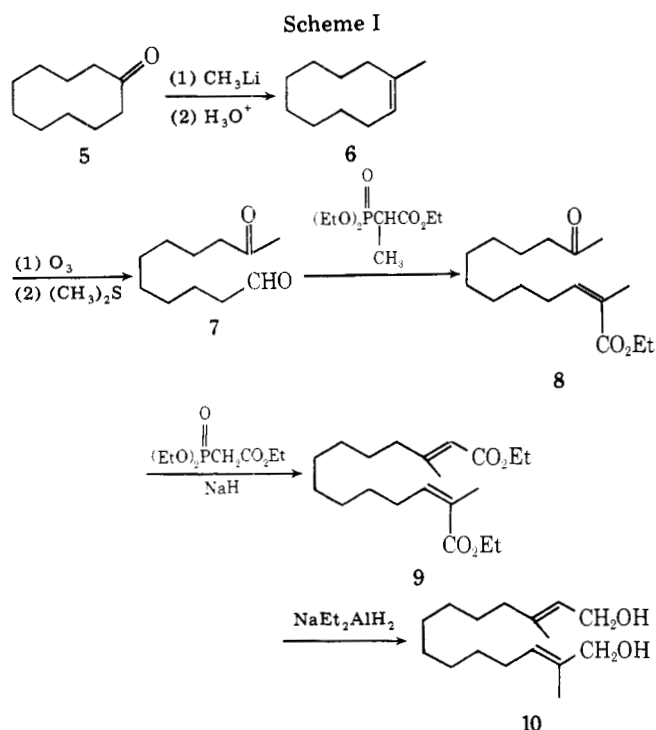
found that direct treatment of allylic or benzylic alcohols with TiCl$_3$/LiAlH$_4$ results in a high yield of coupled dimer.[16] Some of our results are given in Table IV.

Both allylic and benzylic alcohols couple in good yield, and steric hindrance to the coupling of tertiary alcohols is not observed. There are, however, several drawbacks to the reaction. Nonallylic alcohols (n-decanol, cholesterol) do not couple. This is presumably due to the greater strength of the nonallylic C–O bond vs. the allylic C–O bond. A further drawback is that when unsymmetrical alcohols such as farnesol are reduced, coupling can occur with allylic rearrangement, leading to product mixtures. Finally, we have also observed that hydrogenolysis of the hydroxyl occurs as a competing reaction in some cases (for example, farnesol). We ascribe this hydrogenolysis to hydrogen atom abstraction from solvent dimethoxyethane by the intermediate alkyl radical. Recently, both Fujimoto[17] and Baumstark[18] have reported that hydrogenolysis product is found exclusively when a large excess of LiAlH$_4$ is employed in conjunction with TiCl$_4$. Under our conditions, however, in which there is no excess hydride and in which the amount of hydrogenolysis product is solvent dependent (THF and dioxane favor hydrogenolysis relative to dimethoxyethane), we favor solvent donation of a hydrogen atom.

It was clear to us from the outset that this coupling reaction would be much more valuable synthetically if it could be used intramolecularly to form rings. In particular, a number of 14-membered ring diterpenes known as cembranolides have been isolated recently from natural sources. Cembrene itself is a 14-membered ring hydrocarbon first isolated from the Japanese black pine (*Pinus thunbergii*). Cembrene has been synthesized by Dauben by the nickel carbonyl catalyzed intramolecular coupling of a bis(allylic bromide).[19] We were intrigued by the possibility of cembranolide synthesis via titanium-induced intramolecular bis(allylic alcohol) coupling. We therefore synthesized the model diol **10** by the route shown in Scheme I.

Similarly, it might also prove possible to synthesize both elemane sesquiterpenes (1,2-divinylcyclohexanes) and germacrane sesquiterpenes (cyclodecadienes) by appropriate intramolecular couplings. We therefore synthesized bis(allylic diol) **13** as a model by the route shown in Scheme II.

Unfortunately, neither **10** nor **13** gave any detectable
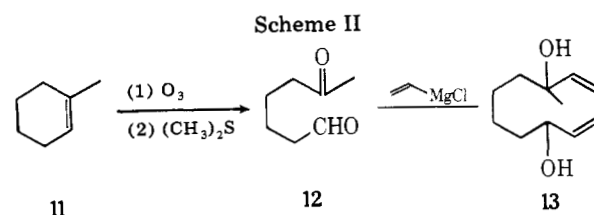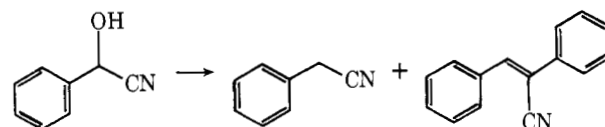
amount of cyclization product when treated with TiCl$_3$/ LiAlH$_4$. Treatment of **10** with TiCl$_3$/LiAlH$_4$ gave a mixture of four products in 80% yield. Analysis by GC/MS clearly showed that all four were isomeric hydrogenolysis products. When **13** was treated with TiCl$_3$ and LiAlH$_4$, a mixture of four hydrogenolysis products was again formed in quantitative yield. These and other attempted intramolecular coupling reactions are presented in Table V. In no case was any cyclization product obtained.[20]
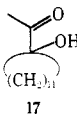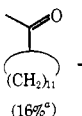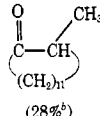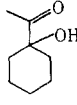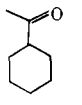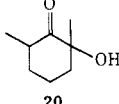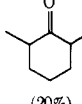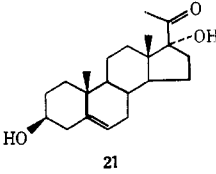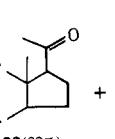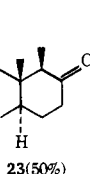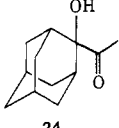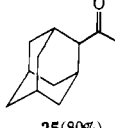
Reduction of Cyanohydrins. If cyanohydrins were to undergo deoxygenation by the general mechanism postulated above, one would expect nitriles to result, and the net effect would be a one-carbon chain extension.
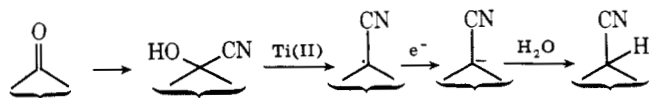
To investigate this possibility, we prepared benzaldehyde cyanohydrin and attempted its reduction with TiCl$_3$/LiAlH$_4$. We observed a complex mixture of products from which phenylacetonitrile could be isolated in 20% yield. In addition, the cyanostilbene was produced (30%). The cyanostilbene presumably arises by condensation of phenylacetonitrile anion with benzaldehyde formed by the reversal of cyanohydrin formation. This loss of HCN was the sole mode of reaction

Table VI. Reduction of α-Hydroxy Ketones with TiCl₄/Zn

α-Hydroxy Ketone		Product (yield)	
17	TiCl₃/LiAlH₄ ⟶	(16%[a])	(28%[b])
	TiCl₄/Zn ⟶ 2-fold excess	(37%)	(37%)
	TiCl₄/Zn ⟶ 5-fold excess	(60%)	(10%)
18	⟶	19(84%)	
20	⟶	(20%)	
21	⟶	22(32%)	23(50%)
24	⟶	25(80%)	

[a] Registry no.: 28925-00-0. [b] Registry no.: 63662-71-5.

when cyclohexanone cyanohydrin was subjected to reduction conditions, and no cyclohexanecarbonitrile was formed. We conclude therefore that mechanistically, cyanohydrin reduction is a feasible process. In practice, however, side reactions render the reaction of no synthetic value.

Reduction of α-Hydroxy Ketones. Analogous to the reduction of cyanohydrins, one might also expect α-hydroxy ketones to undergo direct deoxygenation on treatment with TiCl₃/LiAlH₄. We are aware of no other direct o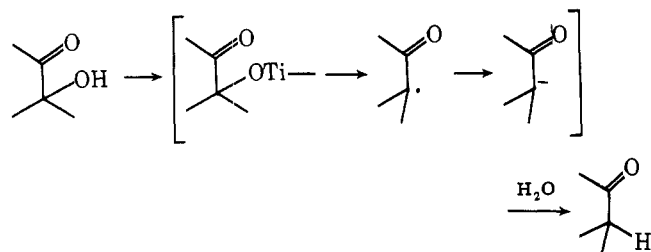ne-step methods for accomplishing this transformation, and the successful reaction should therefore prove valuable. The reaction does in fact take place as expected, although TiCl₃/

LiAlH₄ generally gives rather low yields of product. We found, however, that the low-valent species produced by reducing TiCl₄ with zinc[21] was quite effective and gave good yields in a number of cases. Some of our results are shown in Table VI.

As Table VI shows quite clearly, the deoxygenation of α-hydroxy ketones with TiCl₄/Zn is of limited synthetic use due to the fact that rearrangements often occur. 1-Acetylcyclododecanol, for example, ring expands at approximately the same rate at which reduction occurs. By adding a large excess of reducing agent this problem can be suppressed but not

entirely eliminated. 17-Hydroxy-20-keto steroids also give D-homo rearrangement products in competition with simple deoxygenation. Only in the case of acetylcyclohexanols (where rearrangement to a cycloheptane is unfavorable) does reduction occur smoothly and in good yield. For these cases, however, the reaction is an excellent one. The direct product of the ketol deoxygenation is, presumably, an enolate ion, and the trapping of this ion by electrophiles would effect a net
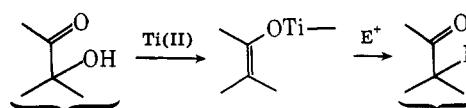
replacement of hydroxyl by carbon. All attempts at trapping the enolate were unsuccessful, however, presumably due to the unusually high strength and low reactivity of the Ti–O bond.

Summary

We have demonstrated that the TiCl₃/LiAlH₄ reagent is effective for carrying out a number of useful reduction procedures. In particular, most epoxides and bromohydrins reduce cleanly to olefins, allylic and benzylic alcohols couple smoothly to dimeric hydrocarbons, and acylcyclohexanols deoxygenate to acylcyclohexanes. These reactions, along with the carbonyl coupling procedure employing active titanium metal,[22] demonstrate the versatility and power of low-valent titanium species as deoxygenating agents in organic chemistry.

Experimental Section

General. Melting points were obtained on a Thomas-Hoover unimelt apparatus. Proton NMR spectra were recorded on a Varian A56/60A (60 MHz) or a Jeolco Minimar (60 MHz) instrument. Chemical shifts are reported in δ (ppm) downfield from internal tetramethylsilane. IR spectra were recorded on Perkin-Elmer 237 or 337 grating spectrophotometers. Gas chromatography/mass spectroscopy was performed on a Finnigan Model 4000 instrument operating at a 70 eV ionization potential and employing a 3% OV-1 on Chromosorb W glass column (4 ft × 0.25 in). TiCl₃ was obtained from Alfa Inorganics and was transferred under an inert atmosphere in a glovebag or a Schlenk apparatus.

The phrase "usual workup procedure" used below means that the reaction mixture was cooled to room temperature, diluted with water, and extracted several times with ether. The combined ether extracts were washed with saturated brine, dried (MgSO₄), and concentrated by solvent removal at the rotary evaporator.

General Procedure for Preparation of Epoxides. A solution of 85% m-chloroperbenzoic acid (0.850 g, 4.20 mmol) in 10 mL of dichloromethane was added dropwise to a stirred solution of olefin (4.0 mmol) in 30 mL of dichloromethane under a nitrogen atmosphere. After stirring for 15 h at room temperature, the reaction mixture was washed with 20% aqueous sodium sulfite and 5% aqueous sodium bicarbonate and then dried (MgSO₄) and concentrated at the rotary evaporator to yield the epoxide product.

General Reaction Procedure for Epoxide Reduction. Lithium aluminum hydride (0.20 g, 5.0 mmol) was added in small portions to a stirred slurry of TiCl₃ (3.08 g, 20.0 mmol) in 60 mL of dry THF under a nitrogen atmosphere at room temperature. Hydrogen evolution was immediate, and the resulting fine black suspension was stirred for 15 min. A solution of epoxide (10 mmol) in 10 mL of dry THF was added in one portion, and the reaction mixture was refluxed for 3 h. After cooling to room temperature, the reaction was worked up in the usual way. In this manner, the following reactions were carried out.

1-Decene from 1,2-Epoxydecane. A 65% yield was determined by GLC (20% SF-96 on GC-22 "Super Support"; 5 ft × 0.25 in) using cyclooctene as an internal standard.

Cyclohexene from Cyclohexene Oxide. A 69% yield was determined by GLC (20% SF-96 on GC-22 "Super Support"; 5 ft × 0.25 in) using cyclooctene as an internal standard.

Cyclooctene from Cyclooctene Oxide. A 53% yield was determined by GLC (20% SF-96 on GC-22 "Super Support"; 5 ft × 0.25 in) using 1-decene as an internal standard.

α-Methylstyrene from α-Methylstyrene Oxide. A 36% yield was determined by GLC (20% SF-96 on GC-22 "Super Support"; 5 ft × 0.25 in) using 1,5-cyclooctadiene as an internal standard.

1-Dodecene from 1,2-Epoxydodecene. A 69% yield was determined by GLC (20% SF-96 on GC-22 "Super Support"; 5 ft × 0.25 in) using 1-decene as an internal standard.

α-Pinene from α-Pinene Oxide. An 11% yield was determined by GLC (20% SF-96 on GC-22 "Super Support"; 5 ft × 0.25 in) using 1-decene as an internal standard.

Cholesterol from 5α,6α-Epoxycholestan-3β-ol. A 75% yield was determined by isolation and crystallization of the product, mp 148 °C.

cis-**5-Decene.** A mixture of 5-decyne (2.00 g, 14.5 mmol) and Lindlar catalyst (0.14 g) in 60 mL of petroleum ether was stirred under 1 atm of hydrogen pressure. Hydrogen uptake (300 mL) ceased abruptly after 1 h. Filtration and solvent removal gave *cis*-5-decene (1.95 g, 96%), pure by GLC (20% SF-96 on GC-22 "Super Support"): NMR (CCl₄) δ 0.7–1.7 (m, 14 H), 1.7–2.3 (m, 4 H), 5.15–5.35 (m, 2 H).

trans-**5-Decene.** A solution of sodium (1.50 g, 65.4 mmol) in 80 mL of liquid ammonia at −78 °C was prepared, and 5-decyne (3.00 g, 18.5 mmol) was added over 20 min. After stirring for 1.75 h, excess sodium was destroyed by cautious addition of aqueous NH₄OH. Ammonia was evaporated, and the reaction was worked up in the usual way to give *trans*-5-decene (2.071 g, 68%): NMR (CCl₄) δ 0.7–1.7 (m, 14 H), 1.7–2.2 (m, 4 H), 5.20–5.45 (m, 2 H).

Deoxygenation of *cis*-5,6-Epoxydecene. A 70% yield of 5-decene was obtained as determined by GLC (20% SF-96 on GC-22 "Super Support"; 5 ft × 0.25 in) using 1-dodecene as an internal standard. The cis/trans ratio of the product could not be determined directly since the isomeric 5-decenes were inseparable by GLC under all conditions tried. We therefore analyzed the product mixture in the following way.

The olefin product mixture was dissolved in 30 mL of dichloromethane and epoxidized with *m*-chloroperbenzoic acid using the general reaction conditions discussed above. After workup, the mixture of *cis*- and *trans*-5-decene oxides was analyzed by GLC (10% Carbowax 20M on GC-22 "Super Support"; 12 ft × 0.25 in). In this manner, a ratio of 21% of *cis*-5-decene to 79% of *trans*-5-decene was determined. The validity of this analytical method was determined by carrying out the appropriate control reaction on a mixture of known composition.

Deoxygenation of *trans*-5,6-Epoxydecane. A 70% yield of 5-decene was obtained. Analysis of the cis/trans product ratio by the method outlined above indicated a ratio of 22% of *cis*-5-decene to 78% of *trans*-5-decene.

General Reaction Procedure for Bromohydrin Preparation. The olefins to be used as substrates were epoxidized according to the general procedure outlined above. A solution of epoxide (4.0 mmol) in 60 mL of CCl₄ was exposed to a slow stream of gaseous HBr for 2 h at room temperature. After washing the reaction mixture with 5% aqueous sodium bicarbonate, the solution was dried (MgSO₄) and concentrated at the rotary evaporator to yield the bromohydrins.

General Procedure for Bromohydrin Reduction. LiAlH₄ (0.142 g, 3.75 mmol) was added to a stirred slurry of TiCl₃ (2.3 g, 15 mmol) in 70 mL of dry THF under a nitrogen atmosphere. Hydrogen evolution commenced, and the resulting black suspension was stirred for 10 min before use. The bromohydrin (5.0 mmol) in 10 mL of THF was added, and the reaction mixture was refluxed for 16 h. After cooling to room temperature, the reaction was worked up in the usual way. In this manner, the following reactions were carried out.

Cyclooctene from *trans*-2-Bromo-1-cyclooctanol. A 96% yield was determined by GLC (5% Carbowax 20M on Chromosorb P; 12 ft × 0.25 in) using 1-decene as an internal standard.

Indene from *trans*-1-Bromo-2-hydroxyindane. A 93% yield was determined by GLC (5% Carbowax 20M on Chromosorb P; 12 ft × 0.25 in) using 1-dodecene as an internal standard.

Cholesterol from 6β-Bromo-3β,5α-hydroxycholestane. A 79% yield was determined by isolation and crystallization, mp 148 °C.

1-Decene from 2-Bromo-1-decanol. A 74% yield was determined by GLC (5% Carbowax 20M on Chromosorb P; 12 ft × 0.25 in) using cyclooctene as an internal standard.

1-Dodecene from 2-Bromo-1-dodecanol. A 91% yield was determined by GLC (5% Carbowax 20M on Chromosorb P; 12 ft × 0.25 in) using indene as an internal standard.

5-Decene from *erythro*-5-Bromo-6-decanol. A 91% yield was determined by GLC analysis (5% Carbowax 20M on Chromosorb P; 12 ft × 0.25 in) using cyclooctene as an internal standard. Analysis of the cis/trans ratio by the epoxide method outlined above showed a ratio of 20% of *cis*-5-decene to 80% of *trans*-5-decene.

5-Decene from *threo*-5-Bromo-6-decanol. An 82% yield was determined by GLC (5% Carbowax 20M on Chromosorb P; 12 ft × 0.25 in) using cyclooctene as an internal standard. The cis/trans ratio was 30% of *cis*-5-decene to 70% of *trans*-5-decene.

General Reaction Procedure for Alcohol Coupling. LiAlH₄ (0.190 g, 5.0 mmol) was added to a stirred slurry of TiCl₃ (2.3 g, 15.0 mmol) in 70 mL of dry dimethoxyethane under a nitrogen atmosphere. The resulting black suspension was stirred for 10 min before use. The substrate alcohol (5.0 mmol) in 10 mL of dry DME was added, and the reaction mixture was refluxed for 16 h. After cooling to room temperature, the reaction was worked up in the usual way. In this manner, the following reactions were carried out.

1,2-Diphenylethane from Benzyl Alcohol. A 78% yield was determined by isolation and crystallization of the product, mp 51–52 °C (lit.[23] mp 52 °C).

2,3-Diphenylbutane from α-Phenethyl Alcohol. A liquid mixture of meso and *dl* products was isolated in 68% yield. Anal. Calcd for C₁₆H₁₈: C, 91.37; H, 8.63. Found: C, 91.59; H, 8.67.

2,3-Dimethyl-2,3-diphenylbutane from 2-Phenyl-2-propanol. A 95% yield was determined by isolation and crystallization, mp 117–118 °C (lit.[24] mp 118–119 °C).

3-(2-Cycloheptenyl)cycloheptene from 2-Cycloheptenol. An 82% yield was determined by chromatographic isolation. Anal. Calcd for C₁₄H₂₂: C, 88.35; H, 11.65. Found: C, 88.14; H, 11.76.

Farnesol coupling gave a mixture of products which was separated by high-pressure liquid chromatography on Porosil A (16 ft × 0.25 in) using petroleum ether as eluent.

Fraction 1 (13%) was assigned structure **3** based on spectroscopic data: IR (CCl₄) 990 and 905 cm⁻¹; mass spectrum, *m/e* 206 (M⁺); NMR (CDCl₃) δ 5.84 (m, 1 H), 5.14 (m, 4 H), 2.05 (m, 7 H), 1.72 and 1.67 (2 singlets, 9 H), 1.31 (m, 2 H), 1.05 (d, 3 H, *J* = 7 Hz).

Fraction 2 (8%) was assigned structure **4** based on spectroscopic data: IR (CCl₄) 1445 and 1365 cm⁻¹; mass spectrum, *m/e* 206 (M⁺); NMR (CDCl₃) δ 5.10 (m, 3 H), 2.00 (m, 8 H), 1.73 and 1.60 (2 singlets, 15 H).

Fraction 3 (48%) was obtained as an inseparable mixture of **1** and **2**: mass spectrum, *m/e* 410 (M⁺). Although squalene itself shows only a single broad vinyl proton absorption center at δ 5.2, careful examination of the NMR spectrum of fraction 3 indicated the presence of an extra ABX vinyl spin system attributed to the monosubstituted double bond in **2**. Careful integration indicated a 2:1 ratio of **1** and **2**.

1-Methylcyclodecene (6). Cyclodecanone (1.0 g, 6.48 mmol) in 5 mL of ether was added to 40 mL of methyllithium solution (1.5 M) under nitrogen. The mixture was stirred overnight at room temperature and then worked up in the usual way. The crude alcohol product was dissolved in 45 mL of hexane and stirred for 16 h at room temperature with 45 mL of 50% aqueous sulfuric acid. The hexane layer was drawn off, dried (MgSO₄), and concentrated to yield **6** (0.99 g, 100%): NMR (CDCl₃) δ 5.14 (t, 1 H, *J* = 8 Hz), 2.24 (m, 4 H), 1.68 (s, 3 H), 1.43 (m, 12 H).

10-Oxoundecanal (7). 1-Methylcyclodecene (0.31 g, 2.04 mmol) was dissolved in 25 mL of methylene chloride and cooled to −78 °C. Ozone (Welsbach ozone generator) was bubbled through the solution until a blue color persisted. Nitrogen gas was then bubbled through the solution for 30 min, and dimethyl sulfide (0.2 g, 3.1 mmol) was added. After stirring at room temperature overnight, the reaction was worked up in the usual way to give 0.34 g (91%) of keto aldehyde **7** as a light oil: IR (neat) 1725 cm⁻¹; NMR (CDCl₃) δ 9.80 (t, 1 H, *J* = 2 Hz), 2.45 (broad t, 4 H, *J* = 6 Hz), 2.15 (s, 3 H), 1.33 (m, 12 H).

Keto Ester 8. Sodium hydride (0.07 g of a 57% mineral oil suspension; 1.59 mmol) was degreased by pentane washings and slurried in 10 mL of DME. Ethyl α-diethylphosphonopropionate (0.36 g, 1.5 mmol) was dissolved in 5 mL of dry DME and added to the NaH suspension. After stirring for 30 min at room temperature, the solution was taken up in a dry syringe and added to a solution of keto aldehyde **7** (0.23 g, 1.27 mmol) in 5 mL of DME. The reaction was stirred for 16 h at room temperature and then refluxed for 1 h. After cooling to room temperature, the reaction was worked up in the usual way to give crude keto ester **8**. Chromatography on silica gel (elution with 10% ethyl acetate–90% pentane) gave 74 mg (22%) of pure **8**: IR (neat) 1710 (broad) and 1650 cm⁻¹; NMR (CDCl₃) δ 6.75 (t, 1 H, *J* = 7 Hz), 4.18 (q, 2 H, *J* = 7 Hz), 2.41 (t, 2 H, *J* = 7 Hz), 2.12 (s, 3 H), 1.82 (s, 3 H), 1.29 (5, 3 H, *J* = 7 Hz).

Diester 9. Sodium hydride (0.14 g of a 57% mineral oil dispersion; 3.31 mmol) was washed with pentane and slurried in 5 mL of DME under a nitrogen atmosphere. Ethyl diethylphosphonoacetate (0.74 g, 3.2 mmol) dissolved in 5 mL of DME was added, and the reaction was stirred for 1 h at room temperature. The resultant solution was drawn into a dry syringe and added to a solution of keto ester **8** (74 mg, 0.28 mmol) in 3 mL of DME. After stirring for 12 h at 85 °C, the reaction mixture was cooled and worked up in the usual way. The crude material was chromatographed on silica gel to give 48 mg (52%) of pure diester **9**: IR (neat) 1700 and 1650 cm⁻¹; NMR (CDCl₃) δ 6.75 (t, 1 H, *J* = 7 Hz), 5.67 (s, 1 H), 4.18 and 4.14 (2 quartets, 4 H, *J* = 7

Hz), 2.16 (s, 3 H), 1.34 and 1.33 (2 triplets, 6 H, *J* = 7 Hz).

Bis(allylic diol) 10. Diester 9 (48 mg, 0.14 mmol) was dissolved in 3 mL of ether and cooled to 0 °C under nitrogen. Sodium diethyl-aluminum dihydride (0.3 mL of a 2.0 M solution in toluene) was added, and the reaction was stirred for 2 h at 0 °C. After workup in the usual way, the crude product was chromatographed on Florisil to give the desired diol 10 (28 mg, 93%): NMR (CDCl₃) δ 5.41 (t, 2 H, *J* = 7 Hz), 4.14 (d, 2 H, *J* = 6 Hz), 3.99 (s, 2 H), 2.02 (m, 4 H), 1.66 (s, 6 H).

Attempted Intramolecular Cyclization of 10. A solution of titanium reagent was prepared as detailed above by mixing TiCl₃ (0.13 g, 0.84 mmol) and LiAlH₄ (0.01 g, 0.28 mmol) in 20 mL of DME. Diol 10 (28 mg, 0.13 mmol) was added, and the mixture was refluxed for 17 h. After workup in the usual manner, the crude product was chromatographed on Florisil to give 19 mg (80%) of a hydrocarbon fraction. Analysis by GC/MS indicated four major components in the product mixture. These components were isomeric and all showed *m/e* 222 (M⁺) corresponding to hydrogenolysis products. No material with *m/e* 220 (M⁺) corresponding to cyclized material, was observed (<1%).

6-Oxoheptanal (12). Methylcyclohexene (1.0 g, 10.4 mmol) was dissolved in 70 mL of methylene chloride and cooled to −78 °C. A stream of ozone was bubbled through the solution until a blue color persisted. A stream of nitrogen was then bubbled through to remove excess ozone, and dimethyl sulfide (1.0 g, 16 mmol) was added. After stirring for 16 h at room temperature, the reaction was worked up in the usual way to give keto aldehyde 12 (1.09 g, 82%) as an oil: IR (neat) 1720 cm⁻¹; NMR (CDCl₃) δ 9.74 (t, 1 H, *J* = 2 Hz), 2.48 (m, 4 H), 2.15 (s, 3 H).

Bis(allylic alcohol) 13. Keto aldehyde 12 (1.09 g, 8.50 mmol) was dissolved in 60 mL of ether under nitrogen, and vinylmagnesium chloride (18.2 mL of a 2.8 M solution) was added. The reaction was stirred for 16 h at room temperature and then worked up in the usual way to give diol 13 (1.50 g, 96%): IR (neat) 3365, 1650, 995, 920 cm⁻¹; NMR (CDCl₃) δ 5.89 (m, 2 H), 5.12 (m, 4 H), 4.08 (d, 1 H, *J* = 6 Hz), 2.43 (s, 2 H), 1.25 (s, 3 H).

Attempted Intramolecular Cyclization of 13. A solution of titanium reagent was prepared as detailed above by mixing TiCl₃ (3.26 g, 21.1 mmol) with LiAlH₄ (0.27 g, 7.0 mmol) in 70 mL of DME. Diol 13 (0.65 g, 3.5 mmol) in 40 mL of DME was added, and the reaction was refluxed for 16 h. After workup in the usual way, the crude product was chromatographed on silica gel to give 0.31 g (60%) of a hydrocarbon product. Analysis by GC/MS indicated four major components. These components were isomeric with *m/e* 152 (M⁺), corresponding to uncyclized hydrogenolysis products. No material with *m/e* 150 (M⁺), corresponding to cyclized product, was observed (<1%).

Reduction of Benzaldehyde Cyanohydrin. A slurry of TiCl₃ (1.56 g, 10 mmol) in 50 mL of DME was treated with LiAlH₄ (0.13 g, 3.8 mmol), and the resulting black suspension was stirred for 10 min at room temperature under a nitrogen atmosphere. Benzaldehyde cyanohydrin (0.417 g, 3.1 mmol) in 10 mL of DME was added, and the reaction was refluxed for 16 h. After workup in the usual manner, the crude product was chromatographed on silica gel to give phenylacetonitrile (55 mg, 15%), identified by comparison with an authentic sample, and 2,3-diphenylacrylonitrile (195 mg, 61%), mp 88 °C (lit.²⁵ mp 88 °C).

1-Acetylcyclododecanol (17) was prepared by the general procedure of Baldwin.²⁶ Thus ethyl vinyl ether (7.38 g, 0.10 mol) was dissolved in 10 mL of dry THF at −78 °C under a nitrogen atmosphere, and *t*-BuLi (35 mL of a 1.6 M solution in pentane) was slowly added over 10 min. The reaction was warmed to room temperature for 0.5 h and then again cooled to −78 °C. A solution of cyclododecanone (9.10 g, 0.050 mol) in 10 mL of THF was added, and the solution was warmed to room temperature for 0.5 h. The reaction was then quenched by addition of aqueous 1.5 N HCl until the water layer remained acidic. Workup in the usual way then provided the crude product which was purified by Kugelrohr distillation (75 °C, 0.05 mm) to give 9.50 g (84%) of impure 17, mp 55–75 °C. Several recrystallizations from pentane provided the pure material (3.6 g, 32%): mp 82–84.5 °C; IR (CHCl₃) 3500 and 1700 cm⁻¹; NMR (CCl₄) δ 2.15 (s, 3 H), 1.50 (s, 22 H).

Acetyladamantanol (24). Ethyl vinyl ether²⁶ (7.58 g, 0.105 mol) was dissolved in 10 mL of THF at −78 °C under nitrogen, and *t*-BuLi (35 mL of a 1.6 M solution) was added slowly by syringe. The reaction was warmed to room temperature for 0.5 h and then again cooled to −78 °C. A solution of adamantanone (6.0 g, 0.04 mol) in 25 mL of THF was slowly added, and the solution was warmed to room temperature for 1 h. The solution was then cautiously acidified with 1.5 N HCl and worked up in the usual way. Crystallization of the residue gave 3.5 g (45%): mp 86.5–88 °C; IR (CHCl₃) 3600 and 1705 cm⁻¹; NMR (CCl₄)

δ 2.10 (s, 3 H); mass spectrum, *m/e* (relative intensity) 194 (M⁺, 1), 151 (100).

General Reaction Procedure for Reducing α-Hydroxy Ketones. TiCl₄ (1.6 g, 8.2 mmol) was dissolved in 2 mL of benzene under a nitrogen atmosphere, and 20 mL of DME was slowly added. Zinc dust (0.39 g, 6.0 mmol) was added, and the mixture was stirred for 45 min at room temperature. The substrate ketol (5.0 mmol) in 2 mL of DME was added, and the reaction was refluxed for 4 h. Workup in the usual way gave the product. In this way, the following reductions were carried out.

Acetyladamantane from Acetyladamantanol. An 80% yield was determined by isolation and crystallization, mp 29.5–31.0 °C.

Acetylcyclohexane from 1-Acetylcyclohexanol.²⁶ An 84% yield was isolated as the 2,4-DNP, mp 140 °C (lit.²⁷ mp 140 °C).

Reduction of 1-Acetylcyclododecanol. The product mixture (70%) was found by GLC (15% XF-1150 on Chromosorb W; 5 ft × 0.25 in) to be a mixture of two products. The major product (58%) was identified as acetylcyclododecanone: IR (CHCl₃) 1700 cm⁻¹; NMR (CDCl₃) δ 2.08 (s, 3 H); mass spectrum, *m/e* (relative intensity) 210 (M⁺, 100), 195 (20), 43 (90). The minor product (12%) was identified as 2-methylcyclotridecanone: IR 1700 cm⁻¹; NMR (CDCl₃) δ 1.25 (s, 20 H), 1.03 (d, 3 H, *J* = 7 Hz); mass spectrum, *m/e* (relative intensity) 210 (M⁺, 80), 195 (2), 99 (100).

2,6-Dimethylcyclohexanone from 2-Hydroxy-2,6-dimethylcyclohexanone. A 20% yield was determined by chromatographic isolation and comparison with an authentic sample.

Reduction of 3β,17α-Dihydroxy-20-ketopregn-5-ene (21).²⁸ The product mixture was separated by column chromatography. The minor product (32%) was identified as 3β-hydroxy-20-ketopregn-5-ene (22) by comparison with an authentic sample. The major product (50%) was assigned structure 23, the D-homo rearrangement product, although we were unable to carry out a complete characterization.

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Titanium-Induced Reductive Coupling of Carbonyls to Olefins

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Active titanium metal, produced in a finely divided form by reduction of $TiCl_3$ with either potassium or lithium, will reductively couple ketones and aldehydes to olefins. Although the intermolecular coupling works best when two identical carbonyls are coupled to a symmetrical product, unsymmetrical couplings can also be carried out in certain cases. The unsymmetrical coupling of a diaryl ketone with another partner is particularly efficient, and a mechanism to account for this is proposed. Intramolecular dicarbonyl coupling to form rings is also possible, and the combination $TiCl_3/Zn$–Cu works best. Rings of size 4–16 and 22 are prepared in high yield. The nature of the active titanium metal is studied by scanning electron microscopy, and a mechanistic proposal accounting for all observed results is presented. It is believed that the coupling reaction occurs on the surface of the active titanium particle.

Recently, three separate research groups independently observed that low-valent titanium reagents ($TiCl_4/Zn$,[1] $TiCl_3/Mg$,[2] $TiCl_3/LiAlH_4$[3]) would reductively dimerize ketones and aldehydes to olefins. Two of these reagent systems[1,2] were reported to be effective only for aryl ketones, while our $TiCl_3/LiAlH_4$ reagent gave excellent yields in both aryl and alkyl cases.[3] Subsequently, a number of research groups used our method to prepare a variety of interesting olefins,[4–9] but, as we have reported,[10] the $TiCl_3/LiAlH_4$ reagent gives capricious results depending on the exact batches of reagents used. Although we have been unable to discover the reason for these capricious coupling results, we have found that the $TiCl_3/LiAlH_4$ reagent does reproducibly effect numerous other organic reductions.[11] We have also found that the carbonyl coupling reaction can be reproducibly carried out using active titanium metal prepared by reducing $TiCl_3$ with 3 equiv of potassium.[10] The results of our study of this Ti^0-induced coupling reaction are presented herein.

Intermolecular Carbonyl Couplings. Significant developments have occurred recently in the preparation of metals in highly active forms.[12,13] Rieke and co-workers, for example, have described a general method for the preparation of highly active metals in finely divided form by reduction of the metal halide with potassium in tetrahydrofuran (THF). Magnesium prepared by this method shows extraordinary reactivity in Grignard reagent formation.[14] We therefore reduced a slurry of $TiCl_3$ in THF with 3 equiv of potassium and observed that the resultant black slurry reductively coupled carbonyl compounds to olefins in high yield. Since the reaction is a heterogeneous one, excess titanium reagent is required and we therefore optimized conditions to find the most efficient procedure. Our results using cyclododecanone as substrate are shown in Table I.

As can be seen in the table (run 2 vs. run 1), heating the reaction for prolonged periods did not increase the yield. The use of either 1 equiv of potassium per $TiCl_3$ (run 4) or 2 (run 3) rather than the theoretical 3 gave markedly lower yields of product. Use of dimethoxyethane (DME) as solvent rather than THF had little effect. Addition of KI to the mixture[14] prior to reduction had little effect. The optimum ratio of $TiCl_3/K$/ketone was 1:3.5:0.25. It became clear in the course

of these optimization experiments that material was being lost during aqueous workup, and we therefore developed a non-aqueous filtration procedure for workup (run 13; see Experimental Section). This modification allowed us to isolate excellent yields (90%) reproducibly.

With optimum conditions established, the coupling of other aliphatic ketones and aldehydes was examined and our results are given in Table II. The coupling reaction is general for aliphatic ketones and aldehydes, and good yields of products are usually obtained. Cycloalkanones of varying ring sizes couple well, and highly hindered olefins (tetraisopropylethylene) can be made in modest yields. The one obvious problem revealed by the results in Table II is that diaryl ketones (fluorenone, benzophenone) couple well, but the products do not survive. The tetraarylethylenes produced reduce further to tetraarylethanes.

It is clear that this Ti^0-induced coupling procedure is an effective one, but the use of potassium to reduce the metal halide, as recommended by Rieke, is a potentially hazardous process. We therefore examined the use of other less reactive alkali metals and were surprised to discover that lithium metal proved as effective as potassium even at temperatures far below its melting point. Thus, heating a slurry of $TiCl_3$ and 3 equiv of Li in DME for 1 h produced a black slurry which effectively coupled carbonyl compounds to olefins. This is a most surprising result for several reasons. In the first place, one would expect the solid lithium pieces to become coated on the surface and rapidly inactivated. This does not appear to happen, however, perhaps due to mechanical agitation by the stirrer. More surprising is the fact that, although the reduction of $TiCl_3$ to Ti^0 is incomplete (much unreacted lithium is recovered), the coupling still proceeds well. We do not know whether lithium is recovered because the $TiCl_3$ is reduced only to Ti(II) rather than Ti^0 or if Ti^0 is actually produced. Considering, however, both the fact that Ti(II) ($TiCl_3$ + 1 equiv of K; run 4, Table II) does not effectively couple alkyl ketones and the fact that Li is a stronger reducing agent than K, we feel that Ti^0 is probably the active species in the $TiCl_3/Li$ reduction. When we investigated the reactivity of $TiCl_3/Li$ for carbonyl coupling, we found that it was generally as effective as $TiCl_3/K$ but was somewhat less reactive in that diaryl ke-