

stabilities of the epimeric carbanions and their relative rates of protonation.

I would like to thank my various co-workers whose names appear in the footnotes. Much of this work was supported by the National Institutes of Health and more recently by the

National Institute on Drug Abuse. I also wish to thank Professor André Rassat and Dr. Valentin Rautenstrauch for helpful and open conversations and/or correspondence concerning these reactions. Finally, this Account was prepared during a sabbatical at Colorado State University; I wish to thank Professor Albert I. Meyers for his hospitality and encouragement.

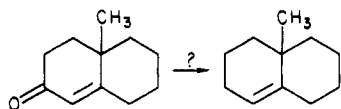
Titanium-Induced Dicarbonyl-Coupling Reactions

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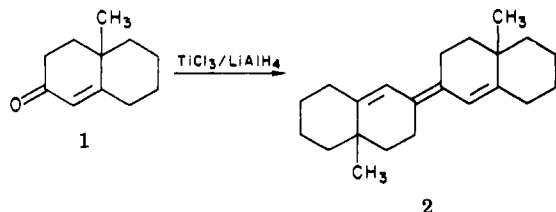
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As often happens in scientific research, our discovery was made by accident. Some years ago we needed to carry out the high-yield transformation of an α,β -unsaturated ketone into the corresponding olefin without migration of the double bond. This kind of transformation often fails with classic methods of ketone deoxygenation such as the Wolff-Kishner reaction or dithioacetal desulfurization, and we therefore sought to devise a new method.



It occurred to us that the ideal method would be a one-pot reaction in which a good hydride donor such as LiAlH_4 might be used in conjunction with an appropriate transition-metal salt. If initial hydride reduction of the carbonyl group were to be followed by strong coordination of the alkoxide anion with the metal, a second hydride delivery might occur in an $\text{S}_{\text{N}}2$ -type fashion, leading to the desired product. In light both of the great strength of the titanium-oxygen bond and of our previous experiences with titanium chemistry,¹ TiCl_3 was the obvious first choice to use in trying out our idea. We therefore prepared a slurry of anhydrous TiCl_3 in tetrahydrofuran (THF), added 0.5 mol equiv of LiAlH_4 , added our enone, and set about determining what had happened.

Just as we had hoped, the product obtained by $\text{TiCl}_3/\text{LiAlH}_4$ treatment of enone 1 was indeed a hydrocarbon, but much to our surprise, a reductive dimerization had occurred, giving an 80% yield of triene 2. The transformation that had occurred—reductive



John McMurry received his B.A. degree in 1964 from Harvard College and his Ph.D. in 1967 from Columbia University where he worked with Gilbert Stork. After 13 years on the faculty of the University of California, Santa Cruz, he moved in 1980 to Cornell University where he is presently Professor of Chemistry. Since 1975 he has made life difficult for countless authors in his capacity as Associate Editor of *Accounts of Chemical Research*.

dimerization of a ketone to yield an alkene—was an unknown reaction at the time although two other groups, led by Mukaiyama² in Japan and Tyrlik³ in Poland, made similar discoveries almost simultaneously.

We immediately recognized that the actual results of our experiment were of potentially far greater significance than the “desired” results, and we therefore began to explore the scope of the new reaction. We soon learned that the reductive coupling reaction was not limited to α,β -unsaturated ketones but was general for all manner of ketones and aldehydes. We also soon learned that many reducing agents besides LiAlH_4 can be used with TiCl_3 in the reaction, and we settled on zinc-copper couple as the safest and most convenient.


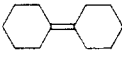
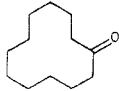
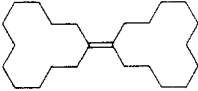

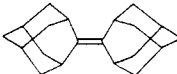
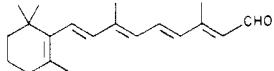
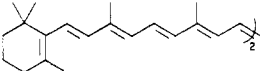

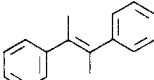
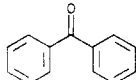
As indicated by the brief list of selected results⁴ given in Table I, the coupling reaction is successful for saturated and unsaturated ketones, saturated and unsaturated aldehydes, aryl ketones and aldehydes, and diaryl ketones. One of the more interesting examples in Table I is the reaction of pentanal (entry 4), which demonstrates that the titanium-induced dicarbonyl coupling normally leads to a cis/trans mixture of olefinic products. Although the more stable isomer predominates, a control experiment has demonstrated that the observed product mixtures are kinetically formed; the titanium reagent does not isomerize olefin geometry. A second interesting result in Table I is the coupling reaction of retinal to yield β -carotene, a substance used as a yellow food-coloring agent and source of vitamin A (entry 5). This high-yield titanium-based synthesis is now licensed for use in the commercial production of β -carotene.⁵

Mechanism of the Titanium-Induced Dicarbonyl-Coupling Reaction

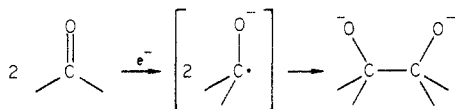
What is the nature of the titanium reagent, and how does the dicarbonyl-coupling reaction occur? We suggested early on⁴ that titanium is present in the form of highly surface-active $\text{Ti}(0)$ particles, a suggestion that has recently received confirmation in careful studies carried out by Geise.⁶ We were also able to show early on that the overall coupling reaction takes place in two

- (1) J. E. McMurry, *Acc. Chem. Res.*, 7, 281 (1974).
- (2) T. Mukaiyama, T. Sato, and J. Hanna, *Chem. Lett.*, 1041 (1973).
- (3) S. Tyrlik and I. Wolochowicz, *Bull. Soc. Chim. Fr.*, 2147 (1973).
- (4) J. E. McMurry, M. P. Fleming, K. L. Kees, and L. R. Krepski, *J. Org. Chem.*, 43, 3255 (1978).
- (5) U.S. Patent 4 225 734.
- (6) R. Dams, M. Malinowski, I. Westdorp, and H. Y. Geise, *J. Org. Chem.*, 47, 248 (1982).

Table I
Titanium-Induced Coupling of Some Ketones and Aldehydes

entry	ketone/aldehyde	product	isolated yield, %
1			86
2			90
3			91
4	CH ₃ CH ₂ CH ₂ CH ₂ CHO	CH ₃ CH ₂ CH ₂ CH ₂ CH=CHCH ₂ CH ₂ CH ₂ CH ₃ (70% trans/30% cis)	77
5			94
6			96
7		Ph ₂ C=CPh ₂	97

steps: (1) an initial carbon-carbon-bond-forming step is followed by (2) a deoxygenation step. The carbon-carbon-bond-forming step is simply a pinacol reaction.⁷ The titanium reagent donates one electron to the ketone to generate a ketyl, which dimerizes, yielding the intermediate pinacol (1,2-diol).



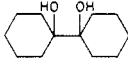
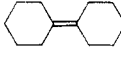
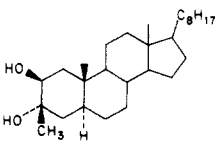
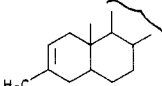



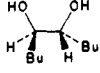
Pinacols can indeed be isolated from titanium-induced couplings if the reactions are carried out below room temperature and are quenched after a brief period of time. Once the pinacols have been isolated, their intermediacy in the olefin-forming reaction can be demonstrated by subjecting them to further treatment with titanium and observing that they are readily deoxygenated to yield olefins. Table II shows some results we obtained⁴ by treating a selection of pinacols with the titanium reagent. Yields during deoxygenations of 1,2-diols are high, and the reactions are of considerable synthetic value. As indicated by the experiments carried out on *meso*- and *d,l*-5,6-decanediol (entries 4 and 5), however, the deoxygenation process is not concerted. Mixtures of *cis/trans* double-bond isomers are produced, starting from stereochemically pure 1,2-diols, though some of the stereochemistry is preserved.

The *second* step in the reaction is the more interesting one. How does deoxygenation of 1,2-diols occur? We probed this question by postulating three possible deoxygenation mechanisms and then designing experiments to distinguish among the three. Scheme I shows the possibilities.

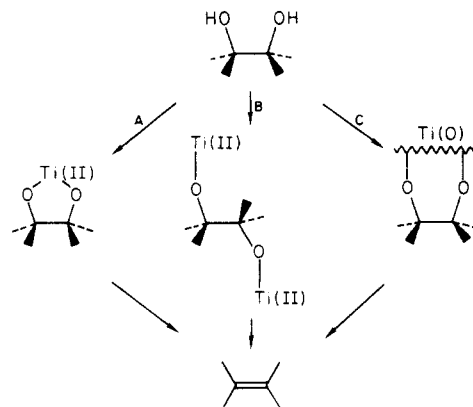
In path A, Scheme I, we suggest that deoxygenation may occur via formation and subsequent decomposition of a five-membered, titanium-containing ring, while in path B, deoxygenation occurs through an intermediate

(7) For a review of the pinacol reaction, see H. O. House, "Modern Synthetic Reactions", 2nd ed., W. A. Benjamin, New York, 1972, pp 167-169.

Table II
Titanium-Induced Deoxygenation of 1,2-Diols to Olefins

entry	1,2-diol	product	isolated yield, %
1			85
2			80
3			55
4		5-decene (60% trans/40% cis)	75
5		5-decene (91% trans/9% cis)	80

Scheme I
Possible Mechanisms for 1,2-Diol Deoxygenation



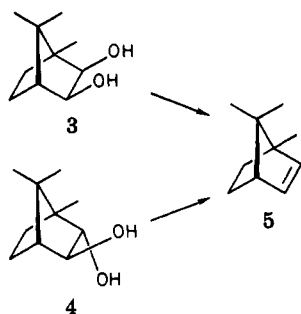
in which the two diol oxygens are bound to different titanium atoms. Path C is less precisely defined than

Table III
 Mixed Titanium-Induced Dicarbonyl-Coupling Reactions

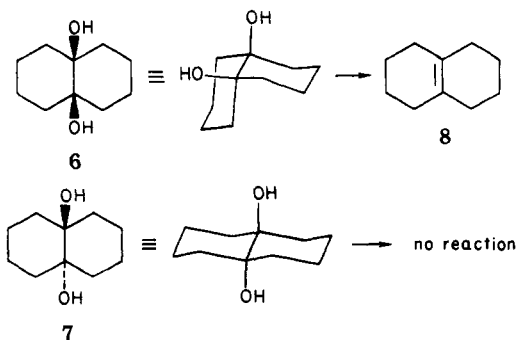
entry	ketones/aldehydes	products	isolated yield, %
1	adamantanone + 4 equiv of acetone	isopropylideneadamantane	63
		adamantylideneadamantane	12
2	cycloheptanone + 4 equiv of acetone	isopropylidenecycloheptane	50
		cycloheptylidene-cycloheptane	26
3	3-cholestanone + 4 equiv of acetone	3-isopropylidenecholestone	54
		3-cholesterylidenecholestone	29
4	acetophenone + 4 equiv of acetone	2-methyl-3-phenyl-2-butene	65
		2,3-diphenyl-2-butene	16
5	benzophenone + 1 equiv of acetone	1,1-diphenyl-2-methylpropene	81
		tetraphenylethylene	14
6	benzophenone + hexanal	1,1-diphenyl-1-heptene	84
		tetraphenylethylene	9
		6-dodecene	8
7	fluorenone + cycloheptanone	cycloheptylidene-fluorene	77
		bifluorenylidene	7
		cycloheptylidene-cycloheptane	17

paths A and B but involves coordination of the diol to the surface of a heterogeneous titanium particle. Cleavage of the two carbon-oxygen bonds then occurs, yielding the olefin and an oxide-coated titanium surface.

Path A could be ruled out by deoxygenation experiments carried out on *cis*- and *trans*-camphanediols, 3 and 4. Angyal showed some years ago⁸ that the *cis* diol 3 reacts with $\text{Pb}(\text{OAc})_4$ nearly one million-fold faster than does the *trans* diol 4. Since the *cis* isomer can easily form a five-membered, lead-containing ring but the *trans* isomer cannot, Angyal interpreted his results as providing evidence for a cyclic intermediate. When we treated the two isomeric diols with our titanium reagent, however, we found that *both* diols reacted at a similar rate to give camphene. Clearly, a five-membered cyclic intermediate is not involved in our reaction.



Path B could also be ruled out by a simple experiment. Treatment of the two isomeric *cis*- and *trans*-9,10-decalindiols, 6 and 7, with titanium revealed an extraordinary difference in behavior. Although the *cis* diol 6 reduced normally and gave the olefin 8 in high yield, the *trans* diol 7 was inert to titanium under all conditions. We interpret this as proof that both oxy-



(8) S. J. Angyal and R. J. Young, *J. Am. Chem. Soc.*, 81, 5467 (1959).

gens of the diol must be able to bind to a common titanium surface, a requirement easily met by the *cis* diol but impossible for the *trans* diol. By elimination, then, we favor path C as the likely route by which our reaction occurs. Strong evidence in support of this suggestion has subsequently been provided by different means through the work of Geise.⁶

Mixed Coupling Reactions

The dicarbonyl-coupling reaction would be of rather limited utility if it were only applicable for the preparation of symmetrical alkenes, and we therefore carried out a study of mixed couplings.⁹ Considering the nature of the carbon-carbon-bond-forming step, a pinacol reaction, we expected to obtain a nearly statistical mixture of symmetrical and mixed coupling products upon treatment of a mixture of ketones with the titanium reagent, and this was, in fact, found. By employing an excess of one component, however, we could obtain good yields of unsymmetrical alkenes. Thus, a coupling reaction on a 1:4 mixture of adamantanone and acetone gave the mixed product, isopropylideneadamantane in 63% yield, along with only 12% of the symmetrical product, adamantylideneadamantane (entry 1, Table III).

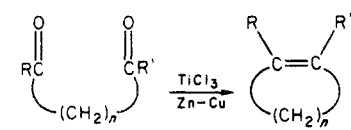
One surprising result of this study was the finding that mixed carbonyl-coupling reactions *do* take place efficiently when one of the partners is a diaryl ketone (entries 5-7, Table III). Presumably, the carbon-carbon-bond-forming step in these couplings is not a ketyl dimerization.⁹ We conclude, however, that the mixed titanium-induced carbonyl-coupling reaction is not of general synthetic use.

Intramolecular Dicarbonyl Couplings

All of the examples discussed up to this point have been intermolecular—two molecules of carbonyl compound have coupled to give an acyclic olefin. Although this is a useful reaction, we felt that an even more important result might be obtained if we were able to carry out intramolecular couplings of dicarbonyl compounds to yield *cyclic* olefins. Such a reaction would be of particular value if medium ($\text{C}_8\text{--C}_{11}$) or large (C_{12} and above) rings could be obtained thereby, since there are few methods capable of preparing such rings. After expending much effort in finding optimum experi-

(9) J. E. McMurry and L. R. Krepski, *J. Org. Chem.*, 41, 3929 (1976).

Table IV
Intramolecular Titanium-Induced Dicarboxyl Couplings



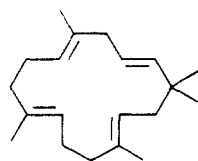
entry	diketone/aldehyde	product	isolated yield, %
1	R = Ph, R' = Ph; n = 2		87
2	R = CH ₃ , R' = Ph; n = 3		70
3	R = CH ₃ , R' = n-C ₇ H ₁₅ ; n = 4		79
4	R = n-C ₅ H ₁₁ , R' = n-C ₅ H ₁₁ ; n = 6		67
5	R = n-C ₅ H ₁₁ , R' = n-C ₅ H ₁₁ ; n = 7		68
6	R = n-C ₄ H ₉ , R' = n-C ₄ H ₉ ; n = 8		75
7	R = n-C ₄ H ₉ , R' = n-C ₄ H ₉ ; n = 9		76
8	R = H, R' = H; n = 10		76
9	R = n-C ₃ H ₇ , R' = n-C ₃ H ₇ ; n = 11		65
10	R = C ₂ H ₅ , R' = C ₂ H ₅ ; n = 12		75
11	R = H, R' = Ph; n = 13		80
12	R = CH ₃ , R' = CH ₃ ; n = 14		90
13	R = CH ₃ , R' = CH ₃ ; n = 20		83

mental conditions, we found¹⁰ that the intramolecular dicarbonyl-coupling reaction can indeed be done successfully. Some of our results are given in Table IV.

We have successfully prepared cycloalkenes of all ring sizes four through 16 and have even prepared a 22-membered ring. All of the reactions took place in good yield, including those that prepared the strained medium-size rings, C₈–C₁₁. Since there are relatively few other methods of macrocyclic ring synthesis, this titanium-induced dicarbonyl coupling should prove to be extremely important in organic synthesis. One experimental detail should be noted, however: all of the results shown in Table IV were obtained under conditions of high dilution. A solution of the dicarbonyl substrate was added to a slurry of the titanium reagent via syringe pump over a 26-h period, thus insuring intramolecular cyclization rather than intermolecular polymerization.

Titanium-Induced Dicarboxyl-Coupling Reactions in Organic Synthesis

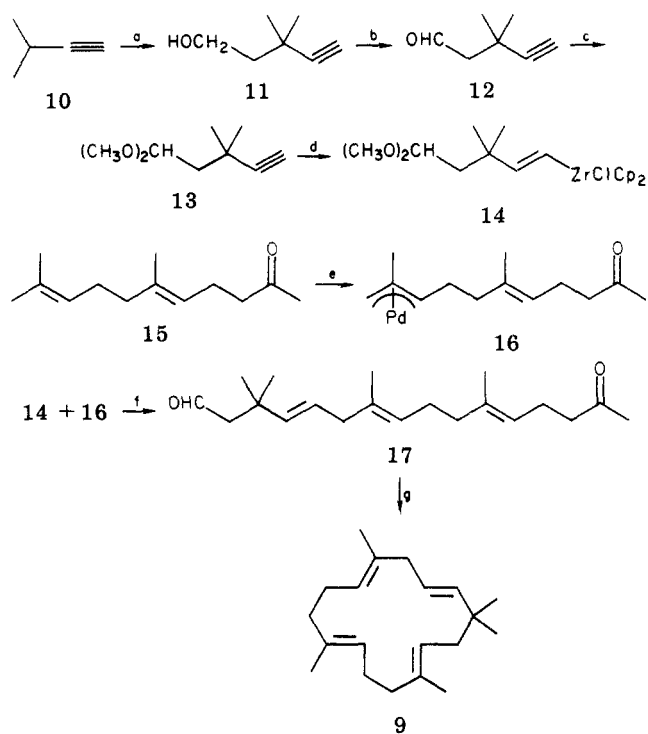
The development of a new synthetic method is of little consequence unless that method can be shown to be of value in solving specific problems and in making accessible certain kinds of structures not otherwise obtainable. We therefore sought to demonstrate the utility of our new reaction in natural product synthesis by preparing a molecule that would be difficult to obtain by other methods. Flexibilene (9), a 15-membered-ring diterpene hydrocarbon isolated from a species of Indonesian soft coral,^{11,12} was chosen as our



flexibilene (9)

bered-ring diterpene hydrocarbon isolated from a species of Indonesian soft coral,^{11,12} was chosen as our

Scheme II^a
Synthesis of Flexibilene, a 15-Membered-Ring Diterpene



^a (a) 2 equiv of n-BuLi, TMEDA, 50 °C, 15 h, ether; then 1 equiv of ethylene oxide, -78 °C, 78%; (b) pyridinium chlorochromate, 69%; (c) (CH₃O)₂CH, CH₃OH, H⁺, 83%; (d) Cp₂ZrClH; (e) Pd(OCOCF₃)₂, 40%; (f) maleic anhydride, CH₂Cl₂, 76%; (g) TiCl₃, Zn-Cu; 52%.

target because of its unique carbocyclic skeleton, because it had not been previously synthesized, and because it would be quite difficult to prepare by known methods.

Flexibilene has four carbon-carbon double bonds, and there are thus four dicarbonyl precursor molecules whose titanium-induced cyclization could, in principle, yield the target. Making a choice of one or the other of these possibilities comes down to planning syntheses of all of them and then selecting the apparently simplest. After considering the four possibilities, we settled on keto aldehyde 17, Scheme II, as the most likely choice. A large part of 17 (carbons 6–16) might be derivable from commercially available geranylacetone (15) by selective functionalization of the terminal *E* methyl group. Alkylation of such a functionalized fragment with a seven-carbon vinyl organometallic piece such as 14 might then lead to the desired keto aldehyde. Of the four double bonds in flexibilene, this plan would allow us to start from a precursor (geranylacetone) having two double bonds of guaranteed stereochemistry, prepare a third double bond stereospecifically by syn hydrometalation of an alkyne, and form the fourth double bond during the titanium-induced cyclization. Our successful route is shown in Scheme II.

Treatment of geranylacetone (15) with palladium bis(trifluoroacetate) gave (π -allyl)palladium complex 16,¹³ and hydrozirconation¹⁴ of alkyne 13 gave vinylzirconium reagent 14. Coupling of these two organo-

(10) J. E. McMurry and K. L. Kees, *J. Org. Chem.*, **42**, 2655 (1977).

(11) M. Herin, M. Colin, and B. Tursch, *Bull. Soc. Chim. Belg.*, **85**, 801 (1976).

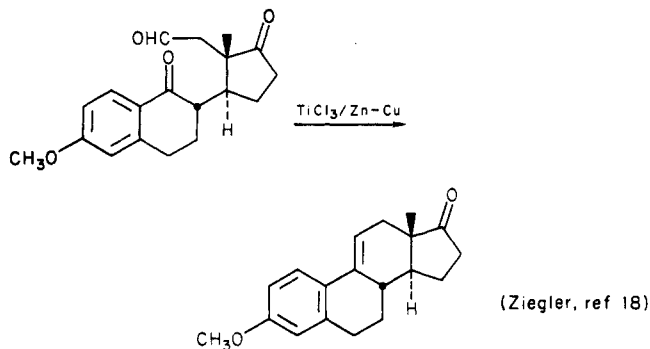
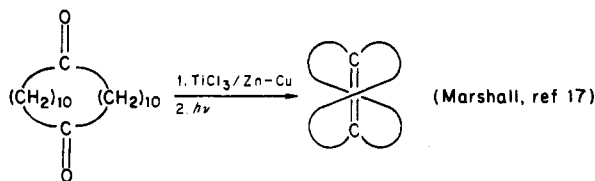
(12) R. Kazlauskas, P. T. Murphy, R. J. Wells, P. Schonholzer, and J. C. Coll, *Aust. J. Chem.*, **31**, 1817 (1978).

(13) B. M. Trost and P. J. Metzner, *J. Am. Chem. Soc.*, **102**, 3572 (1980).

(14) D. W. Hart, T. F. Blackburn, and J. Schwartz, *J. Am. Chem. Soc.*, **97**, 679 (1975).

metallic species under conditions worked out by Schwartz¹⁵ gave the desired keto aldehyde 17 in 76% yield. Titanium treatment of 17 then gave flexibilene in 52% yield, together with 26% of a compound isomeric with flexibilene at the double bond formed during cyclization.¹⁶ Clearly, the titanium-induced dicarbonyl-coupling reaction has proven its worth as a powerful synthetic method. (Although our primary interest in carrying out this synthesis was to demonstrate the key cyclization reaction, we might note parenthetically that this synthesis is an excellent example of the impact that organometallic chemistry is having on organic synthesis. Of the six or so reactions used in the flexibilene synthesis, seven different metals were used at various points—lithium, chromium, palladium, zirconium, titanium, zinc, and copper. Furthermore, of the six reactions, none was even known a decade ago!)

In addition to our own synthetic efforts employing titanium-induced dicarbonyl cyclizations as the key step, other workers have also begun using this methodology. Two of the most elegant such examples are those recently published by Marshall¹⁷ and by Ziegler.¹⁸ Marshall employed titanium-induced dicarbonyl cyclizations as the key step in several of his syntheses of betweenanenes, a new class of twisted cycloalkenes, and Ziegler used such a reaction as a key step in constructing the carbocyclic skeleton of the steroid estrone.



In addition to the above two examples, numerous others have appeared in the literature, and some of the more interesting are listed in Table V. In addition to the highly hindered olefins prepared by titanium-induced dicarbonyl coupling (entries 1 and 2), the reaction has even been used as the key step in synthesizing an organometallic hero sandwich (entry 4).

Our own recent synthesis efforts have been directed toward using the dicarbonyl cyclization as the key step in the synthesis of several decidedly unnatural products. We have recently prepared²⁴ the two smallest members

(15) J. S. Temple and J. Schwartz, *J. Am. Chem. Soc.*, **102**, 7381 (1980).

(16) J. E. McMurry, J. R. Matz, K. L. Kees, and P. A. Bock, *Tetrahedron Lett.*, **23**, 1777 (1982).

(17) J. A. Marshall, M. Constantino, and T. H. Black, *Synth. Commun.*, **10**, 689 (1980).

(18) F. E. Ziegler and H. Lim, *J. Org. Chem.*, **47**, 5229 (1982).

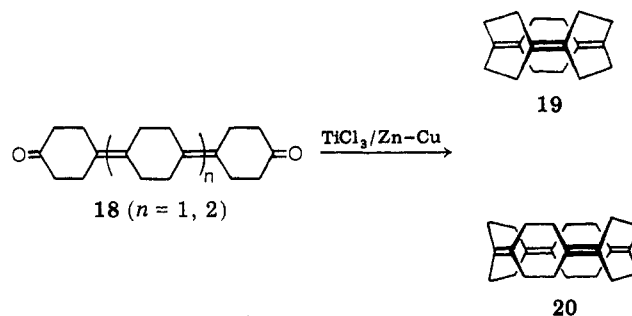
(19) R. F. Langler and T. T. Tidwell, *Tetrahedron Lett.*, 777 (1975).

(20) D. S. Bomse and T. H. Morton, *Tetrahedron Lett.*, 781 (1975).

Table V
Some Examples of Titanium-Induced
Dicarbonyl-Coupling Reactions

entry	ketone/ aldehyde	product	ref
1			19, 20
2			21
3			22
4			23

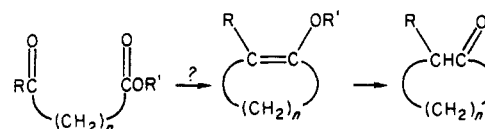
of a series of diketones having the general structure 18. Titanium treatment of 18 where $n = 1$ or 2 yields the large-ring cycloalkenes 19 and 20. These structures



have the p orbitals of their double bonds rigidly held in an orientation such that the inner surface of the molecules are sites of high electron density. We are currently studying the chemistry of these fascinating compounds.

Titanium-Induced Cyclizations of Keto Esters

All of the examples cited thus far have involved reactions of either ketones or aldehydes. What would happen, though, if we were to carry out an attempted cyclization reaction on a keto ester? Since we would be starting out at a higher oxidation state (keto ester vs. diketone), we might also expect to end up at a higher oxidation state (enol ether vs. alkene). Hydrolysis might then yield a cyclic ketone. Such a reaction would greatly extend the power and range of titanium-induced dicarbonyl couplings. As with cycloalkene synthesis, there are few methods currently available for preparing medium- and large-ring cycloalkanones, and a new method could therefore be of great importance.



(21) G. A. Olah and G. K. Surya-Prakash, *J. Org. Chem.*, **44**, 582 (1977).

(22) J. W. Timberlake and Y. M. Jun, *J. Org. Chem.*, **44**, 4729 (1979).

(23) A. Kasahara and T. Izumi, *Chem. Lett.*, 21 (1978).

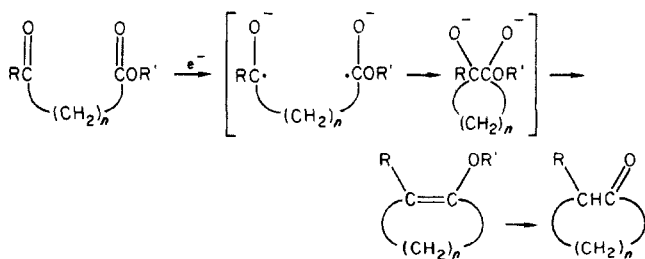
(24) J. E. McMurry and J. R. Matz, unpublished results.

Table VI
Synthesis of Cycloalkanones by
Titanium-Induced Cyclization of Keto Esters

entry	keto ester	cycloalkanone	ring size	isolated yield, %
1	R = <i>t</i> -butyl; <i>n</i> = 1		4	52
2	R = H; <i>n</i> = 2		5	68
3	R = H; <i>n</i> = 3		6	80
4	R = H; <i>n</i> = 4		7	82
5	R = H; <i>n</i> = 5		8	52
6	R = H; <i>n</i> = 6		9	50
7	R = H; <i>n</i> = 11		14	54
8	R = CH ₃ ; <i>n</i> = 8		10	50
9	R = CH ₂ CH ₂ ; <i>n</i> = 9		11	45
10	R = CH ₂ CH ₂ ; <i>n</i> = 10		12	63
11	R = CH ₃ ; <i>n</i> = 11		13	60

We have recently found²⁵ that the keto ester coupling reaction does indeed take place exactly as desired to give cyclic ketones in high yield, and some of our results are given in Table VI. Note that these reactions were carried out with TiCl₃/LiAlH₄ rather than TiCl₃/Zn-Cu, since higher yields were obtained by going to the LiAlH₄-derived reagent. Although the yields of cycloalkanones are generally 10–15% lower than the yields of corresponding cycloalkenes, we have nevertheless been able to establish that the keto ester cyclization is a general reaction. We have prepared rings of all sizes, four (cyclobutanone) through 14 (cyclotetradecanone), and could, presumably, go still higher.

Mechanistically, the titanium-induced cyclization of keto esters appears to be an exact analogue of the diketone cyclization. That is, the reaction occurs in two steps and yields an enol ether as the initial product. Though we do not normally do so, the acid-sensitive enol ether products can be isolated if both the cyclization and the subsequent workup are done under basic conditions.



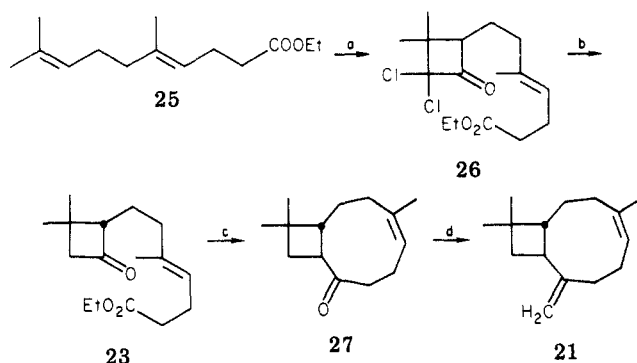
Titanium-Induced Keto Ester Coupling Reactions in Organic Synthesis

Although our discovery of cycloalkanone synthesis by titanium-induced keto ester coupling is yet too newly discovered to have been exploited extensively in organic synthesis, we have recently demonstrated²⁶ its use as

(25) J. E. McMurry and D. D. Miller, *J. Am. Chem. Soc.*, **105**, 1660 (1983).

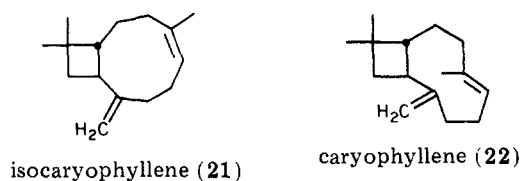
(26) J. E. McMurry and D. D. Miller, *Tetrahedron Lett.*, **24**, 1885 (1983).

Scheme III^a
Synthesis of Isocaryophyllene

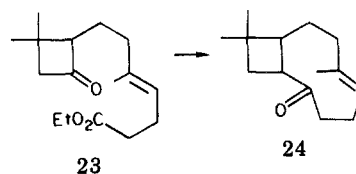


^a (a) Cl₂COCl, POCl₃, Zn-Cu, ether, 75%; (b) Zn-Cu, HOAc, 61%; (c) TiCl₃, LiAlH₄, Et₃N, then H₃O⁺, 38%; (d) Ph₃P=CH₂, Me₂SO, 55%.

the key step in an extremely short synthesis of isocaryophyllene (21).



Isocaryophyllene, a sesquiterpene hydrocarbon isolated from oil of cloves,²⁷ differs from its isomer, caryophyllene (22), only in double-bond stereochemistry. Both compounds have been previously synthesized,²⁸ but isocaryophyllene is the more commercially valuable material because of its use in perfumery. We began our work with the intent of synthesizing caryophyllene, using, as our key step, the intramolecular coupling reaction of keto ester 23 to yield cyclononone 24.



The synthesis of keto ester 23 was accomplished in only two steps by cycloaddition of dichloroketene to ethyl geranylacetate, followed by reduction with zinc in acetic acid (Scheme III). Treatment of 23 with the TiCl₃/LiAlH₄ reagent, however, gave not the expected ketone 24 but the isomeric ketone 27. Methylation of 27 by reaction with methylenetriphenylphosphorane then gave isocaryophyllene.

How does the double-bond isomerization happen? We have never before observed the occurrence of double-bond isomerization in nearly 7 years of work with titanium-induced couplings, and we have shown in a control experiment that caryophyllene itself is stable to the titanium reagent. We believe, therefore, that the isomerization observed in the isocaryophyllene synthesis is unique to the highly strained *trans*-cyclononone ring system and probably takes place when the two

(27) See J. Simonsen and D. H. R. Barton, "The Terpenes", Cambridge University Press, Cambridge, 1952, Vol. 3, pp 39–75.

(28) Isocaryophyllene syntheses: (a) M. Bertrand and J. L. Gras, *Tetrahedron*, **30**, 793 (1974); (b) A. Kumar, A. Singh, and D. Devprabhakara, *Tetrahedron Lett.*, 2177 (1976); (c) A. Kumar and D. Devprabhakara, *Synthesis*, 461 (1976). Caryophyllene synthesis: E. J. Corey, R. B. Mitra, and H. Uda, *J. Am. Chem. Soc.*, **86**, 485 (1964).

carbonyl groups are bound to the titanium particle surface. We do not expect this phenomenon to be a general one and do not expect it to greatly interfere with the utility of the keto ester coupling reaction.

Conclusion and Future Prospects

What began as an accident has now become a reaction of real value in organic synthesis. The titanium-induced coupling reaction of carbonyl compounds allows us to make both symmetrical acyclic olefins from monocarbonyl precursors and unsymmetrical cyclic olefins of all sizes from dicarbonyl precursors. This latter process represents a significant synthetic breakthrough that should continue to lead to the preparation of a large variety of interesting cycloalkenes. Our own continued research on the uses of diketone coupling reactions is leading us in this direction, and we look forward to preparing and studying more unusual compounds such as 19 and 20.

We have also now learned how to extend the dicarbonyl-coupling reaction to the preparation of large-

ring cyclic ketones by titanium-induced cyclization of keto esters. We are continuing to explore this reaction, both in terms of further development as a synthetic method and in terms of use in natural product synthesis. For example, the 14-membered-ring cembrane diterpenes,²⁹ many of which have considerable biological activity, constitute a large class of synthetically untouched natural products that should be amenable to preparation by our new method. We are actively pursuing these possibilities.

I would like to gratefully acknowledge and sincerely thank my co-workers whose names are listed in the references. Only their patience and skill made this work possible. I would also like to thank the Petroleum Research Fund, administered by the American Chemical Society (Grants 7668-AC1 and 11879-AC1), and the National Science Foundation (Grant CHE 76-06141) for their support of this research.

(29) For a review, see: A. J. Weinheimer, C. W. J. Chang, and J. A. Matson, *Fortschr. Chem. Org. Naturst.*, 285 (1978).

Wadsworth-Emmons Reaction Revisited¹

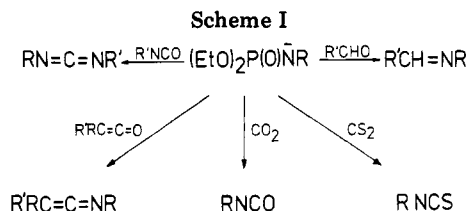
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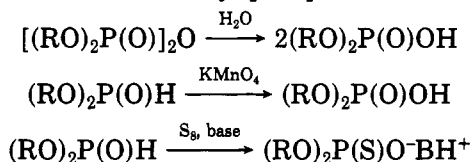
Received July 12, 1982 (Revised Manuscript Received March 14, 1983)

The discovery that organophosphorus ylides and phosphonate anions may interact with carbonyl compounds leading to olefins (Staudinger-Horner-Wittig reaction) had an enormous impact on the development of organophosphorus chemistry. Besides the numerous applications of organophosphorus compounds in organic synthesis, studies on the nature of the Staudinger-Horner-Wittig reaction promoted investigations on the role of pentavalent phosphorus intermediates and on understanding the behavior of hypervalent phosphorus derivatives.² In addition to phosphorus ylides and phosphonates, several phosphoramidates have found broad application as valuable intermediates for the preparation of organic molecules containing the C=N system (Wadsworth-Emmons reaction; Scheme I).³⁻⁵

Although numerous phosphoramidates have been studied, interest in the synthesis of unsaturated C=N systems has overshadowed interest in the fate of the second product of the Wadsworth-Emmons reaction, namely, dialkyl (aryl) phosphates or phosphorothioates. This can be explained by the fact that these compounds can be easily prepared by other methods such as hydrolysis of tetraalkyl pyrophosphates,⁶ oxidation of



dialkyl phosphonates,⁷ and base-catalyzed addition of elemental sulfur to dialkyl phosphonates:⁸



However, the growing interest in the stereospecific synthesis of organophosphates and -phosphorothioates,

(1) Paper dedicated to Professor Georg Wittig on the occasion of his 85th birthday.

(2) G. Wittig and U. Schöllkopf, *Chem. Ber.*, 87, 1318 (1954); L. Horner, H. Hoffmann, and A. G. Wippel, *ibid.*, 91, 61 (1958); G. Wittig in "Organophosphorus Compounds", IUPAC, Butterworths, London 1964, p 245; H. Bestmann in "Phosphorus Chemistry Directed Towards Biology", W. J. Stec, Ed., Pergamon Press, New York, 1980, p 65, and references cited therein.

(3) W. S. Wadsworth, Jr., in "Organic Reactions", Dauben, W. G. Ed., Wiley, New York, 1977, Vol. 25, p 73.

(4) W. S. Wadsworth and W. D. Emmons, *J. Am. Chem. Soc.*, 84, 1316 (1962).

(5) W. S. Wadsworth and W. D. Emmons, *J. Org. Chem.*, 29, 2816 (1964).

(6) A. D. F. Toy, *J. Am. Chem. Soc.*, 70, 3882 (1948); 72, 2065 (1950).

(7) D. Brown and P. Hammond, *J. Chem. Soc.*, 4229 (1960); A. Zwi-
erzak, *Rocz. Chem.*, 39, 1411 (1965).

(8) O. Foss, *Acta Chim. Scand.*, 1, 8 (1947).

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