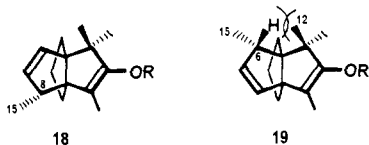


°C, as determined by ^1H and ^{13}C NMR spectroscopy.⁹

The foregoing predictions were borne out when treatment of ketone **8** with *t*-BuOK (15 equiv) and MeI (10 equiv) in THF at room temperature produced **11** (mp 88 °C) and **12** (mp 91 °C) in 68% and 17% yields, respectively, after flash chromatography. Furthermore, in accord with the previous analysis, when **12** was resubmitted to the alkylation conditions it was recovered unchanged.¹⁷

Introduction of the fourth methyl group (C15) required for modhephene was accomplished by reaction of vinylcyclopropyl ketone **11** with LiMe_2Cu (5 equiv; THF, -78 °C), which proceeded with complete stereoselectivity and with exclusive 1,5-addition to provide, after in situ enolate trapping,^{18,19} **16** in 76% yield.²⁰ The unusual regiochemical selectivity (1,5-addition favored over 1,7-addition^{21,22}) observed in this reaction can be explained on the basis of product development control. Thus, in the transition state leading to **19** (R = metal cation) via either an $\text{S}_{\text{N}}2'$ or a



reductive elimination mechanism,²² quaternization of C6 would be accompanied by development of a significant steric interaction between the C6 hydrogen and the C12 methyl group. This effect would be absent during quaternization of C8 in the event of 1,5-addition. This interpretation was supported by molecular mechanics calculations using Allinger's MM2 program,²³ which indicated that enol **19** (R = H)²⁴ has 4.7 kcal/mol more strain energy than enol **18** (R = H).

Completion of the synthesis involved reduction (Li^0 , EtNH_2 , *t*-BuOH, THF, 0 °C)¹⁶ of the now readily available (five steps) propellane phosphorodiamidate **16**, which furnished **17** in 93% yield. Finally, selective hydrogenation of **17** quantitatively provided (\pm)-modhephene (**4**), spectroscopically identical with authentic samples of natural and synthetic material kindly provided by Professors Zalkow and Smith.²⁵

In summary, this synthesis, proceeding from indan and vinyl acetate in seven steps and in 8.2% overall yield, presents a concise solution to the modhephene problem and the basis for the extension of the arene-olefin cycloaddition to other problems in propellane synthesis. Further studies are in progress.

Acknowledgment. This work was supported by grants (CA21136 and CA31845) awarded by the National Cancer Institute, DHHS.

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(24) Enols **18** and **19** (R = H) were used as models for the corresponding enolates.

(25) We thank Professor A. B. Smith, III (University of Pennsylvania) for providing samples of natural (via Professor Zalkow; see ref 6a) and synthetic (see ref 7a,b) modhephene.

Registry No. (\pm)-**4**, 76739-64-5; (\pm)-**5**, 83060-51-9; (\pm)-**6**, 83060-52-0; (\pm)-**7**, 83043-45-2; (\pm)-**8**, 83043-46-3; **9**, 83043-47-4; **10**, 51027-89-5; (\pm)-**11**, 83043-48-5; (\pm)-**12**, 83043-49-6; (\pm)-**15a**, 83043-50-9; (\pm)-**16**, 83043-51-0; (\pm)-**17**, 83043-52-1; (\pm)-**18**, 83043-53-2; (\pm)-**19**, 83043-54-3; (\pm)-**20**, 83043-55-4; vinyl acetate, 108-05-4; indan, 496-11-7; lithium dimethylcuprate, 15681-48-8.

Titanium-Induced Reductive Elimination. Syntheses of 1,3-Dienes¹

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van Tamelen and his co-workers Schwartz,² Hanzlik,³ and Sharpless³ showed that low-valent titanium can be used to effect reductive coupling of benzylic² and allylic alcohols.³ Subsequently, low-valent titanium has been employed in the pinacolic coupling of carbonyls and in the reductive coupling of carbonyls to olefins.⁴ Reductive elimination of 1,2-glycols to olefins⁵ as well as the cyclization of 1,3-glycols to cyclopropanes⁶ have also been reported. We now report that low-valent titanium reacts with 2-ene-1,4-diols and a 2-yne-1,4-diol to yield 1,3-dienes by a 1,4-reductive elimination reaction (Scheme I).

(*E*)- and (*Z*)-1,2-bis(1-hydroxycyclohexyl)ethylene were conveniently prepared from readily available 1,2-bis(1-hydroxycyclohexyl)acetylene. Catalytic hydrogenation over a Lindlar catalyst⁷ produced the pure *Z* isomer and reduction of the acetylenic diol with lithium aluminum hydride⁸ yielded the *E* isomer. Refluxing a tetrahydrofuran solution of either the *E* or the *Z* diol for 3 h with an excess of the low-valent titanium (2-4:1 molar ratio) yielded dicyclohexylideneethane in 75% and 70% yields, respectively. Since dicyclohexylideneethane is a key moiety of vitamin-D, this result suggests that this mode of generating 1,3-dienes might be effectively used in the syntheses of vitamin-D's and their analogues.^{9,10}

Low-valent titanium reagents have been prepared by reduction of TiCl_3 or TiCl_4 with metals⁴⁻⁶ such as magnesium, potassium, sodium, lithium, zinc-copper couple, or metal hydrides, particu-

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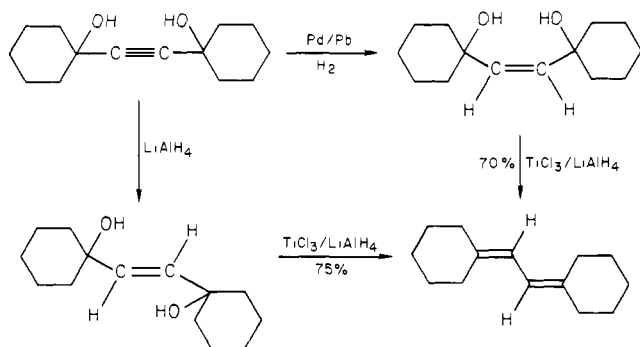
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Scheme I

Table I. Reduction of (*E*)- and (*Z*)-2-Ene-1,4-diols to 1,3-Dienes

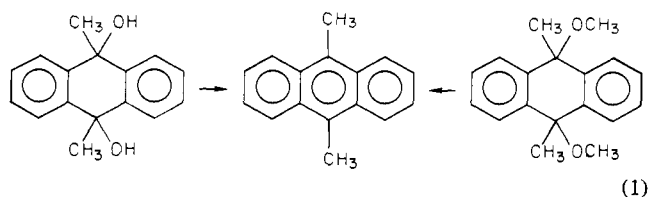
R ¹	R ²	R ³	R ⁴	isomer	molar ratio TiCl ₃ : diol	diene ^a yield, %
-(CH ₂) ₅ -	-(CH ₂) ₅ -	-(CH ₂) ₅ -	-(CH ₂) ₅ -	<i>Z</i>	4:1	70
-(CH ₂) ₅ -	-(CH ₂) ₅ -	-(CH ₂) ₅ -	-(CH ₂) ₅ -	<i>E</i>	4:1	75
CH ₃	CH ₃	CH ₃	CH ₃	<i>Z</i>	4:1	62 ^b
CH ₃	CH ₃	CH ₃	CH ₃	<i>E</i>	4:1	78
Ph	Ph	Ph	Ph	<i>Z</i>	4:1	42 ^{b,c}
Ph	Ph	Ph	Ph	<i>E</i>	3:1	83
Ph	H	Ph	H	<i>Z</i>	2.5:1	75 ^d

^a Identity of all products was established by IR, ¹H-NMR spectra, and comparison with reported data. ^b On the basis of the ¹H NMR spectrum, all other yields are isolated yields. ^c A 26% yield of the cyclization product, 2,3,5,5-tetraphenyl-2,5-dihydrofuran, was also obtained. ^d *E,E*-isomer isolated.

larly lithium aluminum hydride. A mixture of TiCl₃ and LiAlH₄ (4:1) is known as the McMurry reagent. However, Geise¹¹ has found that the TiCl₃:LiAlH₄ ratio of 2:1 is the most effective, at least in the coupling of ketones, and therefore this reagent was used in this study.¹²

As can be seen from Table I, the yields of diene are very good. This plus the fact that the starting 2-ene-1,4-diols are easy to obtain—condensation of an aldehyde and/or ketone with acetylene followed by reduction—holds promise that this reaction might lead to a general method for the syntheses of 1,3-dienes.

The diol is not essential for the reaction to occur. The monomethyl as well as the dimethyl¹³ ether of (*Z*)-2,5-dimethyl-2,5-dihydroxy-3-hexene also gives rise to the corresponding 2,5-dimethyl-2,4-hexadiene in 82% and 64% yields, respectively. Moreover, both 9,10-dimethyl-9,10-dihydroxyanthracene and the dimethyl ether gave quantitative yields of 9,10-dimethylanthracene by reaction with low-valent titanium (eq 1).

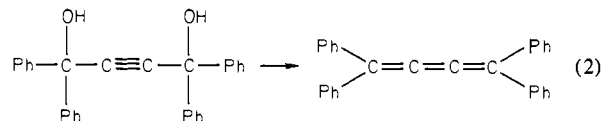


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(13) This experiment was performed by C. J. Franson.

Furthermore, in an analogous reaction, 1,1,4,4-tetraphenyl-1,4-dihydroxy-2-butyne was reduced to the stable 1,1,4,4-tetraphenyl-1,2,3-butatriene in 83% yield (eq 2).



The general scope, limitations, and mechanism of this reaction^{14,15} are under active investigation, especially concerning the use of other low-valent metals to effect these transformations.

(14) To our knowledge the only other example of converting a 2-ene-1,4-diol to a 1,3-diene directly, but in inferior yields, is that reported by Kuhn and Wallenfels (Kuhn, R.; Wallenfels, K. *Ber. Dtsch. Chem. Ges.* **1938**, *71*, 1889) by using P₂I₄ or VCl₂ as reducing reagents. A 2-yne-1,4-diol has been reported to yield a 1,3-diene in 35% yield upon treatment with lithium aluminum hydride: Naylor, P.; Whiting, M. C. *J. Chem. Soc.* **1954**, 4006. For a list of reagents used to convert 2-yne-1,4-diols to cumulenes see: Murray, M. in "Methoden der Organischen Chemie" (Houben-Weyl-Müller), 4th ed.; Verlag: Stuttgart, 1977; Vol. 5, 2a.

(15) **General Procedure. Preparation of Reducing Agent.** A suspension of 3.12 g (20 mmol) of TiCl₃ in 60 mL of dry THF was cooled to 0 °C, and 380 mg (10 mmol) of LiAlH₄ was added via a Schlenk tube in small portions. The resulting black mixture was stirred at 0 °C for 30 min and then refluxed for an additional hour.

Reduction of 2-Ene-1,4-diol. To the black suspension, cooled to 0 °C, was added 5.0 mmol of diol. After the hydrogen evolution subsided, the reaction mixture was refluxed for 3 h. The reaction mixture was cooled, 40 mL of 2 N hydrochloric acid was added, and the mixture was extracted with chloroform. The chloroform extract was washed with water and dried over anhydrous magnesium sulfate. The chloroform was stripped to yield either a solid, which was then recrystallized, or an oil, which was purified by distillation.

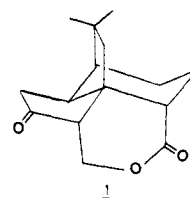
Mechanism and Regioisomeric Control in Palladium(II)-Mediated Cycloalkenylations. A Novel Total Synthesis of (±)-Quadrone

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The direct, intramolecular cycloalkenylation of an enol derivative is a powerful strategy for construction of bridged polycyclic systems, but one that has been hitherto unavailable to the synthetic chemist. We have recently discovered a Pd(II)-mediated cycloalkenylation of silyl enol ethers that offers the first solution to this gap in synthetic methodology.¹ We now report observations bearing on the mechanism and scope of this cyclization and exploit these findings in a remarkably short total synthesis of the tetracyclic antitumor agent (±)-quadrone (1).²



To elucidate the mechanism of our cycloalkenylation reaction, we have compared the behavior of the enol ethers 2a-c with 1.0 equiv of Pd(OAc)₂ in dry MeCN for 4 h at room temperature

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