

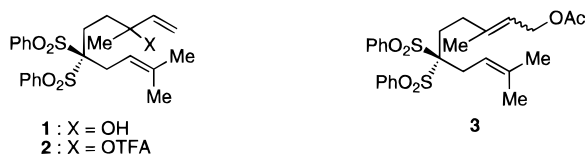
Synthesis of (\pm)-10-*epi*-Elemol by a Highly Stereoselective Intramolecular Palladium-Catalyzed Coupling of an Allylstannane with an Allyl Acetate

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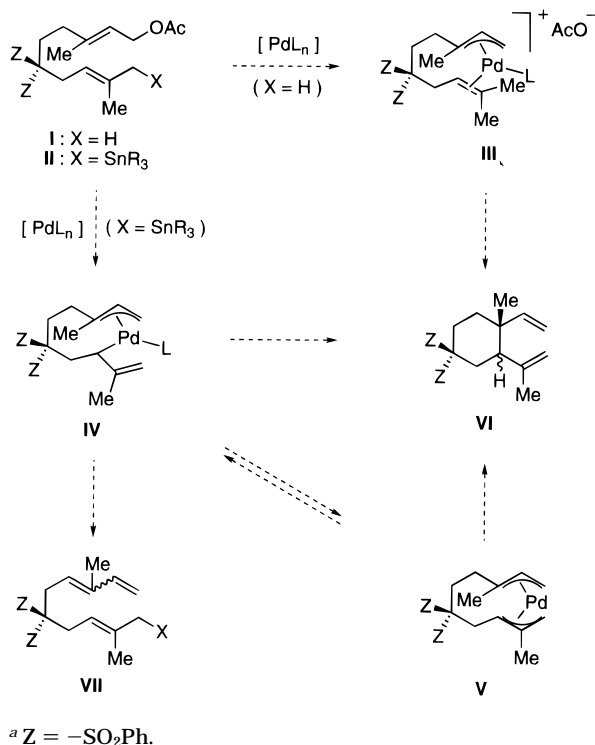
Received July 30, 1997 (Revised Manuscript Received September 16, 1997)

The potential of nickel-promoted allyl/allyl coupling for the construction of sesquiterpenes was early demonstrated by Corey in the syntheses of (\pm)-elemol.^{1,2} However, the regio- and stereoselectivity of this coupling is rather low, and the reaction requires a stoichiometric amount of the metal complex Ni(CO)₄. The alternative intramolecular insertion of (η^3 -allyl)palladium complexes into alkenes allows for the efficient synthesis of five- or six-membered ring carbocycles (Scheme 1).^{3,4} However, increasing the steric hindrance by introduction of methyl groups at C-3 of the allyl and the alkene termini in substrates of type I leads to recovering of unchanged starting materials under catalytic conditions. Thus, substrates **1–3**,⁵ which could give rise to (η^3 -allyl)palladium complexes by oxidative addition to Pd(0),⁴ failed to cyclize under all the conditions examined. This failure



is most probably a consequence of the instability of complex **III** due to the lower coordination ability of the trisubstituted alkene to Pd(II) (Scheme 1). Therefore, we decided to examine the prospect of effecting the cyclization of substrate **II** by an intramolecular palladium-catalyzed cross-coupling of an allylstannane with an allyl acetate.⁶ This coupling could proceed through complexes **IV** or **V**,^{7,8} which would suffer reductively elimination to give carbocycle **VI**.⁹ However, precedents for this second approach were not particularly encouraging since this type of Stille coupling reaction is limited to allyl substrates that cannot eliminate to form a conjugated diene such as **VII**.^{6,10} In fact, Keinan has recently shown that

Scheme 1^a



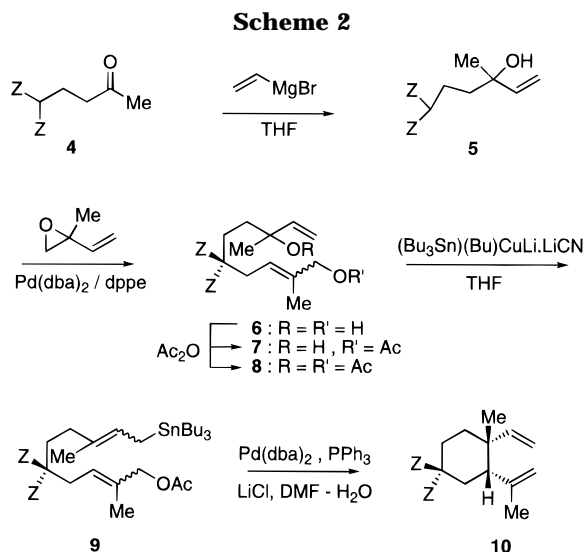
this facile β -elimination proceeds from intermediates of type **IV** through a concerted pathway, probably via a six-electron six-center transition state.¹¹

Herein we wish to report that, despite the ample precedent for elimination in the reaction of allyl stannanes with allylic electrophiles,^{6,11} the intramolecular coupling outlined in Scheme 1 could be efficiently carried out. The presence of water in the solvent was shown to be a key parameter for the success of this transformation. Furthermore, the stereoselectivity of this process was exceptionally high, allowing for the efficient preparation of *epi*-elemol (**17**),¹² a rare member of the elemene family of sesquiterpenes bearing cis vinyl and isopropenyl groups.

The synthesis of the required precursor for the cyclization was completed by using organometallic transformations in all but one step (Scheme 2).^{5b} Reaction of keto disulfone **4**¹³ with vinylmagnesium bromide gave **5** (87%), which was allowed to react with isoprene epoxide in the presence of a palladium catalyst¹⁴ to give **6** as a 1:1 mixture of *E/Z* isomers (97%).¹⁵ Acetylation of **6** afforded either **7** (pyridine catalyst, 79%) or **8** (DMAP catalyst, 80%). Stannane **9** was efficiently prepared in 79% yield

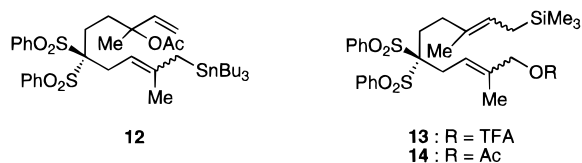
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(8) The cyclization could also proceed through a (η^1 -allyl)(η^3 -allyl)palladium complex regioisomeric to **IV** or a bis(η^1 -allyl)palladium complex in equilibrium with **IV** and **V**.

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^a Z = -SO₂Ph.

from diacetate **8** by a highly regioselective reaction with a mixed cuprate.¹⁶ The desired carbocyclization was effected in the presence of Pd(dba)₂ catalyst (10 mol %),¹⁷ PPh₃ (20 mol %), and excess LiCl in 0.5% aqueous DMF at 80 °C for 20 h to give **10** as a single isomer in 91% yield. The presence of water in the solvent^{10b} and the addition of LiCl¹⁸ were essential for the success of the reaction. The reaction could also be performed in the absence of PPh₃, although a full equivalent of palladium was required under these conditions.¹⁹



Carbocycle **10** probably arises by cyclization of bis(η^3 -allyl)palladium complex *syn-V* in preference to *anti-V*, which would yield stereoisomer **11** (Scheme 3). The stereoselectivity of this reaction cannot be easily explained by steric hindrance arguments,²⁰ and it may be the result of an electronic preference for an endo cyclization pathway. The participation of bis(η^3 -allyl)palladium complexes is strongly supported by the fact that **12**,^{5b,21} a regioisomer of **9**, also afforded **10** in the palladium-catalyzed coupling process. In contrast, allylsilanes **13** and **14**^{5b,22} failed to yield any cyclization derivative under all the conditions examined.²³ This failure is probably due to the reduced nucleophilicity of these 3,3-disubsti-

(15) Alternatively, **6** was obtained in five steps as follows: (i) palladium-catalyzed reaction of bis(phenylsulfonyl)methane and isoprene epoxide (98%); (ii) protection of the alcohol as THP derivative (89%); (iii) ruthenium-catalyzed Michael addition to methyl vinyl ketone (100%);¹³ (iv) addition of vinylmagnesium bromide (74%); (v) acid-catalyzed methanolysis of the THP protecting group (76%).^{5b}

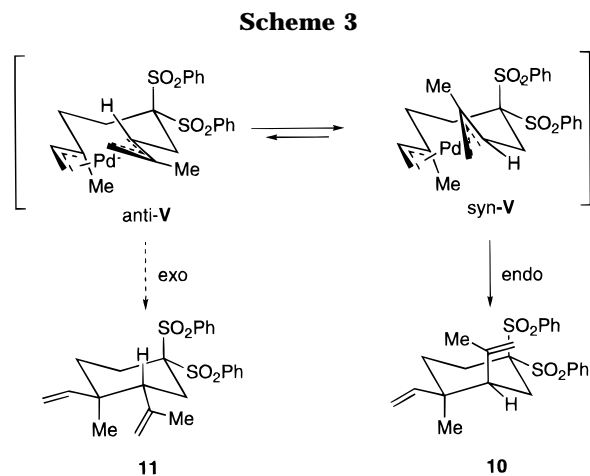
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(17) The actual complex has the formula [Pd₂(dba)₃·dba] (dba = dibenzylideneacetone): Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnett, J. J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, *65*, 253.

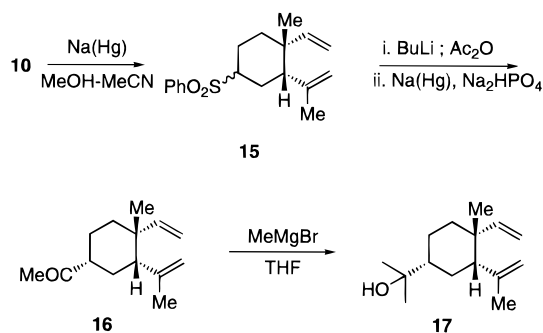
(18) (a) The use of LiI, CuI, or K₂CO₃ as the additives gave negative results. (b) For the role of halide ions on the oxidative addition of Pd(0) complexes, see: Amatore, C.; Azzabi, M.; Jutand, A. *J. Am. Chem. Soc.* **1991**, *113*, 8375.

(19) Similar results were obtained by using NMP as the solvent. Pd(PPh₃)₄ and Pd(dba)₂/PCy₃ were also active catalysts.

(20) The monosulfone derived from **9** by reductive elimination and acetylation affords **15** after palladium-catalyzed cyclization a mixture of C-1 epimers identical with that obtained by desulfonation of **10** (Scheme 4).



Scheme 4



tuted silanes toward external attack to the (η^3 -allyl)palladium intermediate.

The stereochemistry of **10** was demonstrated by its transformation into naturally occurring 10-*epi*-elemol (**17**)¹² (Scheme 4).^{5b} Thus, reductive desulfonation of **10** afforded **15** (74%),²⁴ whose anion was acetylated to give, after reductive desulfonation, **16** (95%)²⁴ as a 9:1 mixture of α -ketone epimers. Final reaction of **16** with methylmagnesium bromide afforded racemic **17** (82%).^{12,25}

In summary, this work shows that, contrary to that observed in the intermolecular coupling of allylstannanes with allyl acetates,^{6,11a} the intramolecular reaction leads to the clean formation of a carbon-carbon bond. The stereoselective cyclization of bis(η^3 -allyl)palladium complex **V** was unexpected and suggests that the synthesis of carbocycles bearing 1,2-*cis* dialkenyl substituents could be general by this method. Further work on this issue is in progress.

Acknowledgment. This work was supported by the DGICYT (Project PB-94-0163). We also thank Johnson Matthey PLC for a generous loan of palladium dichloride. J.M.C and M.M. acknowledge the receipt of fellowships by the Comunidad Autónoma de Madrid and the *Ministerio de Educación y Cultura*, respectively.

Supporting Information Available: Experimental details and characterization data for new compounds (16 pages).

JO9714021

(21) This substrate was prepared via the Michael reaction of [5,5-bis(phenylsulfonyl)-2-methyl-2-pentenyl](tri-*n*-butyl)stannane with methyl vinyl ketone.^{13,5b}

(22) These silanes were prepared by silylation of the corresponding trifluoroacetates with (Me₃Si)₂: Tsuji, Y.; Funato, M.; Ozawa, M.; Ogiyama, H.; Kajita, S.; Kawamura, T. *J. Org. Chem.* **1996**, *61*, 5579.

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(24) Based on unrecovered starting material.

(25) For previous syntheses of **17**, see: Taber, D. F.; Wang, Y. *Tetrahedron Lett.* **1995**, *35*, 6639 and references therein.