

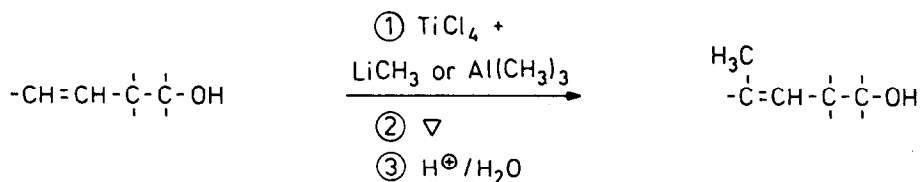
SOLVENT-CONTROLLED ADDITIONS OF
 ORGANOTITANIUM REAGENTS TO OLEFINIC DOUBLE BONDS

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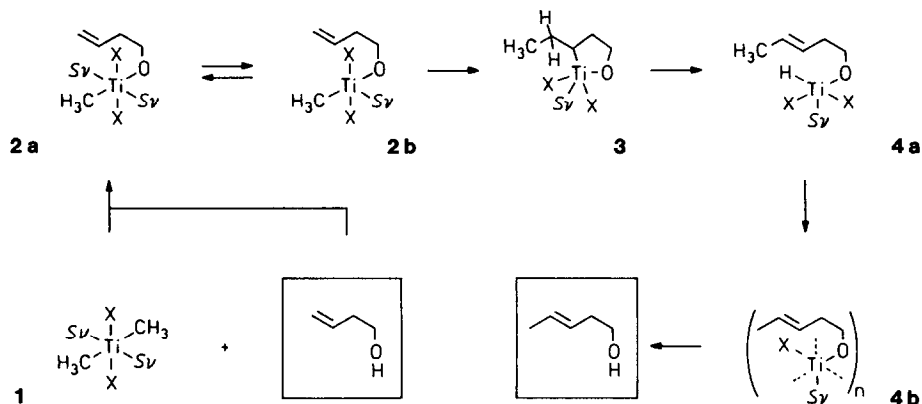
Summary: Under carefully chosen working conditions (solvent, temperature), methyltitanium reagents smoothly convert homoallyl alcohols having a terminal double-bond into (E)-3-penten-1-ols whereas non-terminal 3-alken-1-ols afford 4-methyl-branched derivatives with configurational inversion of the chain (Z → E; E → Z), stereoselectivities being better than 99%.

Recently we have disclosed a procedure for the titanium-mediated methylation of homoallyl alcohols [1] the conditions of which we ourselves qualified as "devoid of any elegance" [2]. After mixing of the reagent with the substrate and evaporation of the solvent, heating of the viscous residue to a minimum temperature of 120°C for at least 3 h was found necessary to accomplish the desired δ-hydrogen/methyl substitution in a presumed addition/elimination sequence. Yields were moderate and, worse, in several cases imperfect typo-, regio- or stereo-selectivities were observed.

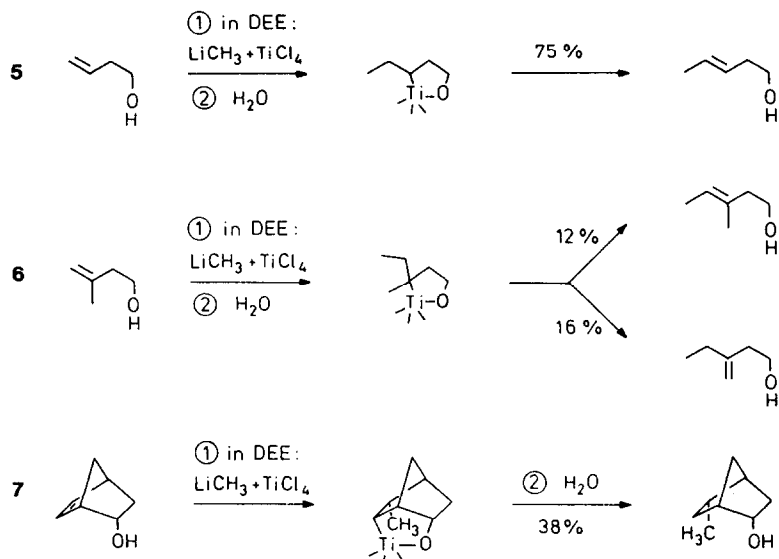


Any attempt to improve the method must explicitly deal with the crucial role that the solvent plays in organotitanium reactions. In hydrocarbon or chlorohydrocarbon media 3-buten-1-ol appears to react, though at low temperature, more or less randomly, the 3-penten-1-ols (mainly *trans*) being formed with a maximum yield of 32% and being accompanied by up to 35% hydrogenation products [3]. In ethereal solvents titanium reagents such as 1 (in general, X = Cl) [4] should exist as monomeric species and hence favor more selective transformations. On the other hand, the intramolecular addition of an alkenyloxy-attached methyltitanium moiety to the olefinic double bond requires coordinative unsaturation at the metal. In other words, adduct 2a must first loose (at least) one solvent molecule and become 2b before the rate-limiting step can

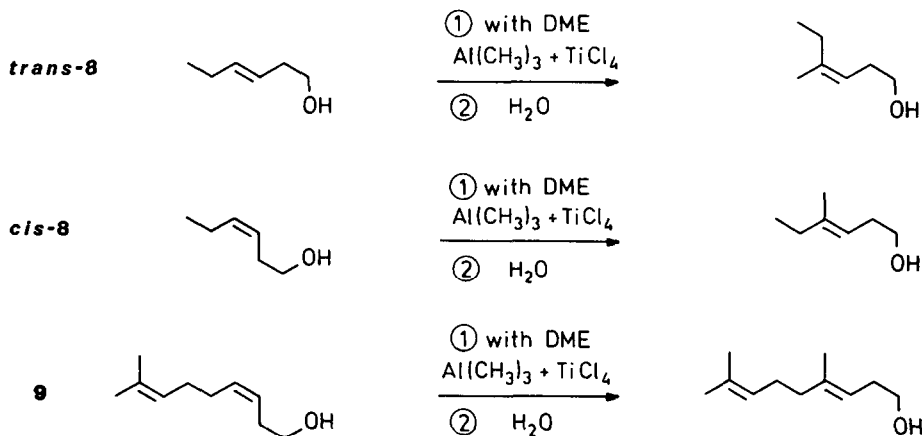
take place to produce **3**. The subsequent hydride transfer (\rightarrow **4a**), elimination of hydrochloric acid (or any other H-X) [5] and oligomerization (or polymerization) of the resulting Ti(II) species (\rightarrow **4b**) are fast processes that require no further activation.



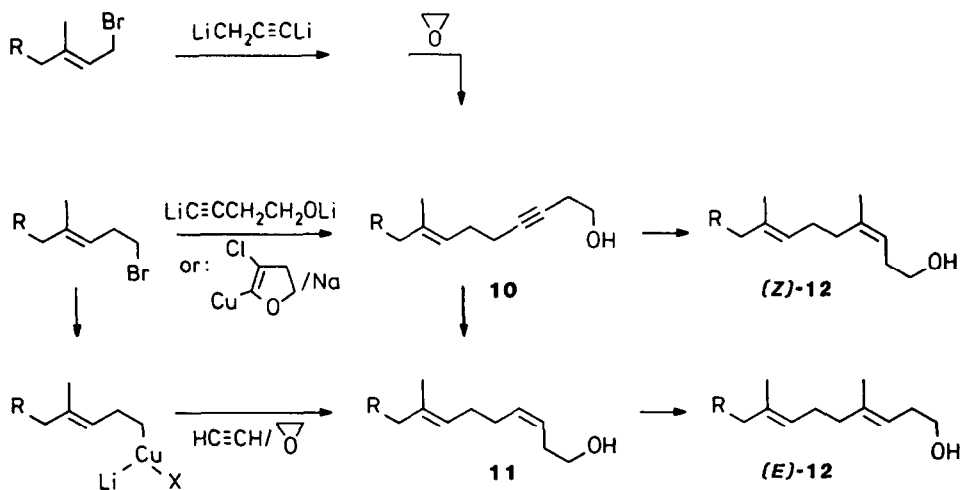
Due to its extreme "oxyphilicity" [6], titanium binds ethers very tightly. Tetrahydrofuran can only be removed at high temperatures ($> 120^{\circ}\text{C}$) unless reduced pressure is applied. The chelating ethyleneglycol dimethyl ether is even more strongly retained; in its presence titanium reagents are almost inert. In contrast, diethyl ether (DEE) complexes with metals much more loosely and may be easily replaced. Thus, we found the titanium-mediated methylation of homoallyl alcohols to occur in this solvent even at 25°C . Substrates having a terminal, vinylic double-bond such as 3-buten-1-ol (**5**) afford homologated (*E*)-3-alken-1-ols with satisfactory yields ($\sim 75\%$) and stereoselectivity ($\sim 98\%$). As the proposed mechanism would have predicted, 3-methyl-3-buten-1-ol (**6**) or any other 3-alkyl-substituted substrate gives rise to two regioisomeric products while with norborneol (**7**) the reaction stops at the adduct stage, no intramolecular hydride transfer being possible within the rigid bicyclic structure.



In diethyl ether, however, only poor stereoselectivities ($Z/E \sim 10 : 90$) can be achieved if homoallyl alcohols having *internal* double bonds are employed as the substrates. Much better results ($Z/E < 1 : 99$) are achieved in pentane solutions which contain small amounts of dimethyl ether [7]. Starting with, respectively, *trans*- and *cis*-3-hexen-1-ol (*trans*- or *cis*- 8), both (*Z*)- and (*E*)-4-methyl-3-hexen-1-ol were isolated after 3 h at 20°C in 55% and 60% yield. In the same way, *cis*-8-methyl-3,7 nonadien-1-ol (9) gave (*E*)-4,8-dimethyl-3,7-nonadienol ("homogeraniol", 80%).



The last example demonstrates a remarkable synthetic potential of organotitanium reagents for a "non-natural" assembling of isoprene units. A $C_{(5n)}$ - or $C_{(5n)+1}$ -precursor can be chain-elongated to a key alkynol of type 10 by using C-nucleophiles such as dilithio-propyne [8], 4-lithiooxy-1-butynyl-lithium [9] or 2-(3-chloro-4,5-dihydrofuran-2-yl)-copper [10]. Then, alkynol 10 may be directly treated with organotitanium compounds, following the procedure of Thompson [11], to give the (*Z*)-homoterpenoid (*Z*)-12. Alternatively, it may be submitted to partial hydrogenation and the resulting *cis*-3-alken-1-ol 11 (also accessible by consecutive addition [12] of acetylene and oxirane to the respective $C_{(5n)+1}$ -copper reagent) finally converted into the stereoisomeric homoterpenoid (*E*)-12.



Acknowledgment. This work was supported by the Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung, Bern (grant nr. 2.635-0.82).

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- [4] Structure 1 is only shown for clarity. In reality, we add titanium tetrachloride as the last reagent and hence produce immediately 2a or an analog thereof.
- [5] The acid thus released inevitably consumes one additional equivalent of methyllithium (or trimethylaluminum) which gets converted into methane.
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(Received in Germany 18 June 1985)