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$TiCl_4$ promoted reaction of aldehydes with 1,5-dienyl allylsilanes: addition accompanied by cyclization

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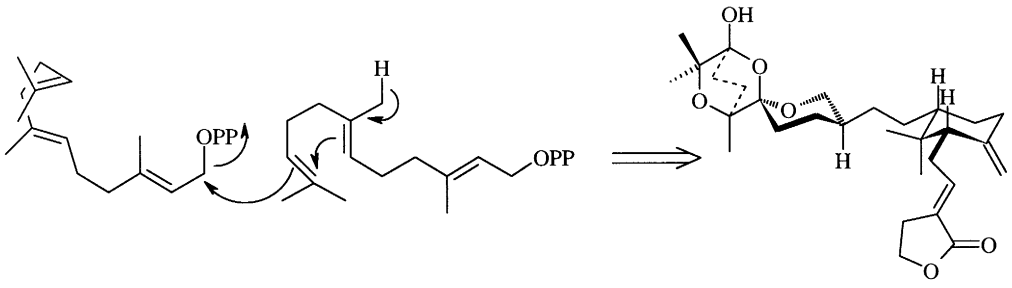
Abstract

$TiCl_4$ readily promotes the addition of 1,5-dienyl allylsilanes to aliphatic aldehydes with concomitant cyclization to afford 1,3-*cis*-disubstituted methylenecyclohexanes with remarkable stereoselectivity. The trimethylsilyl group exerts a strong activating and directing influence on the regioselectivity and stereoselectivity of this biomimetic cyclization.

Keywords: biomimetic reactions; cyclization; aldehydes; dienes.

Many isoprenoid natural products are biosynthesized via a polyolefinic electrophilic cyclization. The initiation of ring closure is usually caused either by protonation of the terminal double bond or by opening of a terminal epoxide.[1] However, there is an increasing number of compounds for which biogenetic cyclization of an acyclic precursor is achieved by C–C bond formation of the terminal double bond with a carbenium ion. For example, the structural framework of saponaceolides suggests that their biosynthesis may involve direct coupling of two farnesyl units accompanied by cyclization (Scheme 1).[2,3] A similar pathway has been recently proposed for the monocyclic triterpenoid mispyric acid.[4] An intramolecular variant of this mechanism gives rise to the verticillane skeleton, a putative intermediate



Scheme 1.

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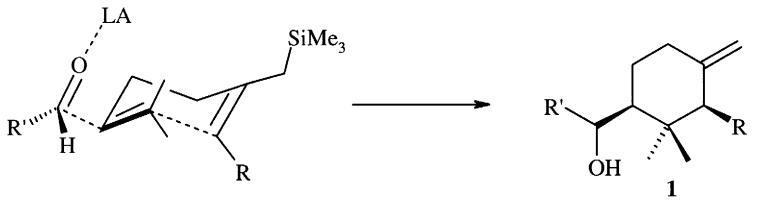
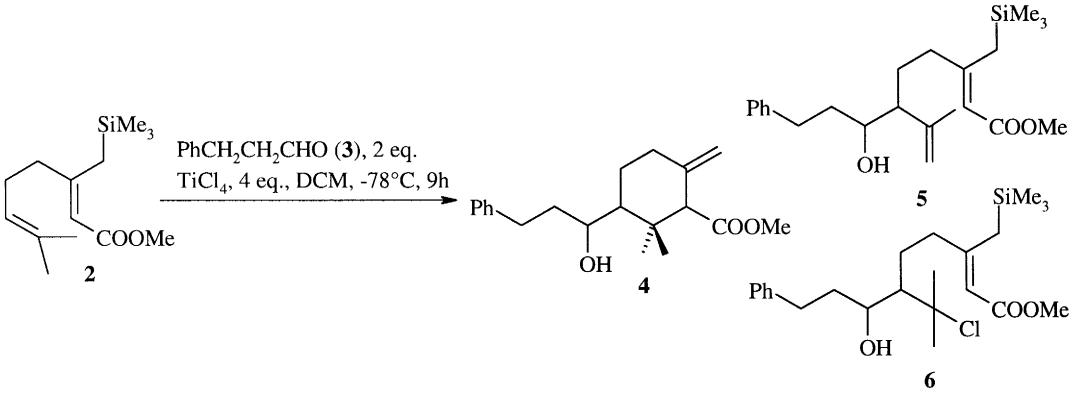
along the biosynthetic pathway to Taxol®.[5] From a synthetic point of view, early studies have shown that Friedel–Crafts reactions of geranyl derivatives with acyl chlorides may mimic this kind of diene cyclization rather efficiently; however, diastereo- and regioselectivity were far from being satisfactory.[6–8] In parallel studies, Julia carried out a prenylation–cyclization reaction of isoprenoid polyolefins that was initiated by alkylation of the distal double bond with isoprene epoxide under anhydrous $ZnCl_2/MeNO_2$ conditions[9] or with an allylic alcohol under CF_3COOH catalysis;[10] unfortunately, under these conditions a mixture of stereoisomeric prenylated compounds are also produced. We reasoned that the low stereoselectivity was possibly due to a non-concerted mechanism for the alkylation–cyclization steps and better diastereomeric excesses could therefore be achieved if the carbenium species developing at the tertiary carbon of the terminal double bond could be readily intercepted by the other double bond of the diene system. To this purpose, in principle an allyl silane could function adequately. In fact, the allyl silyl group has been used as an effective terminating unit in electrophilic polyolefinic cyclizations by a number of groups[11] even if, to the best of our knowledge, none of them involved cyclizations promoted by an external carbenium species. In addition to providing a reactive electron-rich double bond, a trialkylsilyl moiety can efficiently control the regioselectivity of the cyclization to yield the exocyclic olefin. Here, we report our preliminary results on the Lewis acid promoted alkylation–cyclization reaction of aldehydes with 1,3-dienyl allylsilanes (Scheme 2).



Scheme 2.

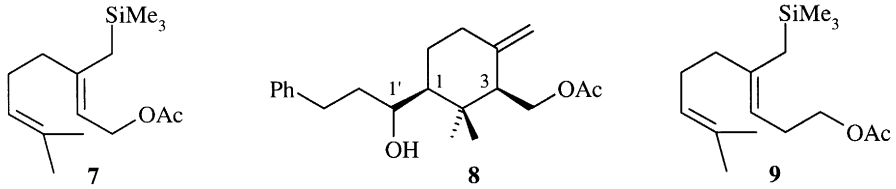
We started our experiments by examining the reaction between the easily available dienyl ester **2**[12] and aldehyde **3**, taken as model compounds. It was readily found that a C–C bond formation with a concomitant ring closure occurred smoothly using $TiCl_4$ as Lewis acid; however, the desired compound **4** (mixture ca. 2:1 of stereoisomers at the carbinol centers)[13] was obtained in only 5% yield, while the ene compound **5** (30%, dr >10) and the corresponding chloride **6** (10%, dr >10) were the most abundant products (Scheme 3).[13] Looking for a more electron-rich allyl silane, we then considered the reaction between **3** and dienyl acetate **7** in the presence of $TiCl_4$. After some optimization, we found that the biomimetic-like cyclization could be effected in a still moderate but more satisfactory 35% yield (40%



Scheme 3.

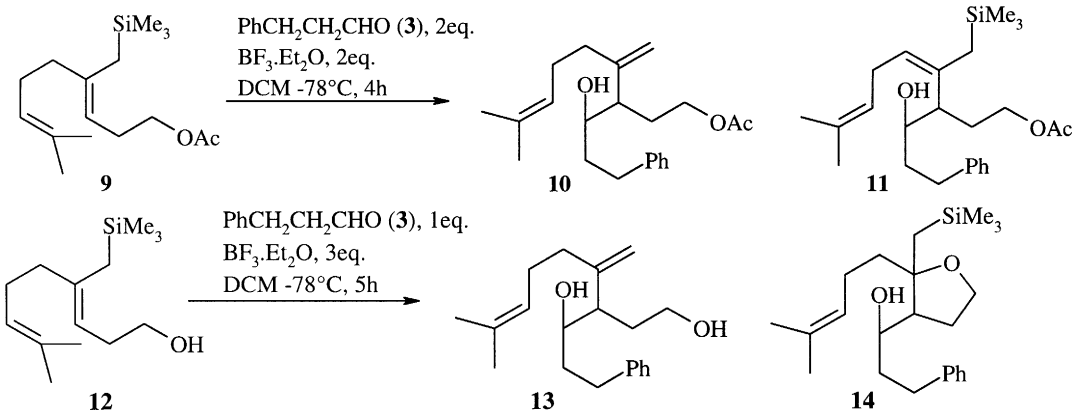
on recovered starting aldehyde). The C-1′ epimers **8** (ratio of 2.3:1, undetermined stereochemistry at the carbinol center) having the two 1,3-substituents *cis* oriented (NOE experiments), constituted the 90% of the cyclization products, while the corresponding *trans* disubstituted diastereoisomeric alcohols accounted for the remaining 10%.

In order to explore the generality of the method, the reaction was then extended to diene **9**[14] and other aldehydes, including hexanal, nonanal, isovaleraldehyde and benzaldehyde. With the exception of the latter compound, for which no alkylation was observed, the other aldehydes gave the expected cyclic products of general formula **1** (R and R′ substituents as appropriate) in consistent yields (30–35%) and diastereomeric excesses (80–85%).



A general procedure follows: $TiCl_4$ (freshly distilled from CaH_2) in anhydrous CH_2Cl_2 (1 M solution, 2 equiv.) was added by syringe to a solution of aldehyde (1.5 equiv.) in anhydrous CH_2Cl_2 at −78°C under an argon atmosphere. The mixture was kept at −78°C for 10 min, then a solution of the allyl silane (1 equiv.) in anhydrous CH_2Cl_2 was added. Stirring was continued at −78°C until disappearance of the diene (30 min–1 h). The solution was quenched with saturated $NaHCO_3$, diluted with CH_2Cl_2, and washed with saturated NaCl. Drying (Na_2SO_4) and concentration of the organic layer gave a crude mixture that was separated by flash silica gel column chromatography (gradient of EtOAc in hexanes) to afford the desired cyclic products.

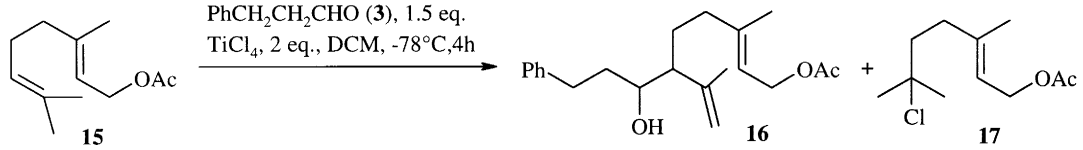
Interesting results were obtained when boron trifluoride etherate was used as a Lewis acid promoter instead of $TiCl_4$. The reaction of aldehyde **3** with diene **9** was much slower and afforded the acyclic compounds **10** (26% yield; dr 4) and **11**(17% yield, undetermined dr) (Scheme 4).[13] The former is the product of the Sakurai reaction[15] of the allyl silane unit, while the latter is formed by the ene reaction on the electron rich double bond of **9**. If the free alcohol **12** was used as diene component of the reaction, the ene product **13** (12% yield, dr 3.8) was accompanied by the tetrahydrofuran derivative **14** (20% yield, undetermined dr) arising from interception of the developing carbenium species by the nucleophilic hydroxy group.[13]



Scheme 4.

At present, we have no firm explanation for the strikingly different directing influence of the two Lewis acids on the regioselectivity of these reactions; we assume it to be due, at least in part, to the different hardness of the carbon of the coordinated carbonyl group and to the well-known diverse coordinative properties of $TiCl_4$ and BF_3.

In order to confirm the essential role of the allyltrimethylsilyl group in promoting the cyclization step, we performed the reaction between aldehyde **3** and geranyl acetate **15** under the above standard conditions (Scheme 5). As anticipated, no cyclization occurred; instead, the product of the ene reaction **16** (dr >10) and chloride **17** were formed in 46 and 14% yield, respectively.[13]



Scheme 5.

In conclusion, the preliminary results described here show clearly that $TiCl_4$ promotes a quite efficient biomimetic-like addition–cyclization reaction of aliphatic aldehydes with 1,3-dienyl allyl silanes. 1,3-*cis*-Disubstituted methylenecyclohexanes are thus produced with remarkable stereoselectivity. Further studies on the optimization of the reaction as well as on the application in the biomimetic synthesis of natural products will be reported in due course.

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