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Stereoselective synthesis of all-*trans* methyl substituted polyenes by reductive elimination and application to the synthesis of all-*trans* 3-methyl-nona-2,4,6-trienol

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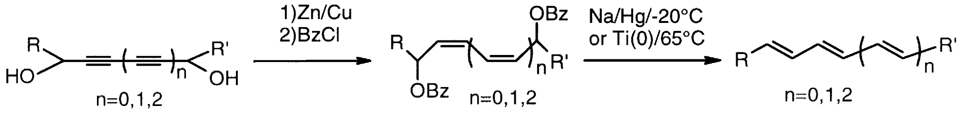
Abstract

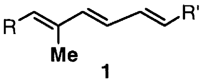
The stereoselective synthesis of all-*trans* 3-methyl-nona-2,4,6-trienol **2** by reductive elimination of the corresponding 1,6-dibenzoate-2-methyl-2(*Z*),4(*Z*)-diene is described. This result shows that reductive elimination can be extended to the formation of all-*trans* methyl substituted polyenes which are present in many natural products biosynthetically made from isoprenic units. © 2000 Elsevier Science Ltd. All rights reserved.

In our previous studies[1] on stereoselective polyene synthesis, we reported that all-*trans* dienes, trienes and tetraenes could be prepared by Na(Hg) or low valent titanium reductive elimination of 1,4-dibenzyloxy-2-alkenes or 1,6-dibenzyloxy-2,4-dienes or 1,8-dibenzyloxy-2,4,6-trienes[2] (Scheme 1).



Scheme 1.

This synthetic method was applied to the preparation of many natural products containing a triene unit such as (6*E*,5*S*,12*R)* and (5*S*,12*R*) leukotriene B_4,[3] haminol 1,[4] isobretonine A[5] and also to the synthesis of the methyl ester of β-parinaric acid[2c] with a tetraene unit. However, all these molecules have unsubstituted polyenes. Many natural products, biosynthetically made from isoprene units, contain conjugated all-*trans* methyl substituted polyenes. The basic unit **1** is included in a very large number of important molecules.



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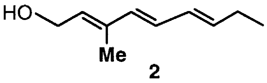

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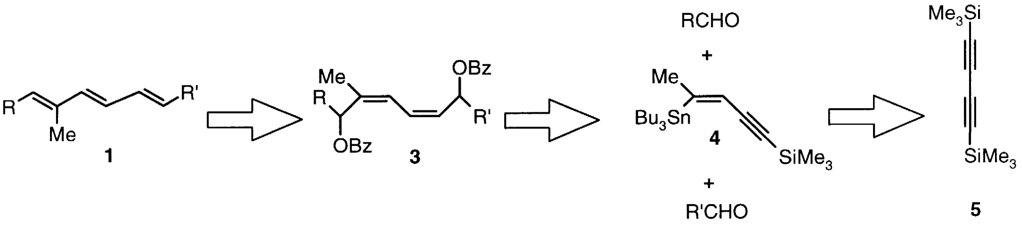
We report in this paper the stereoselective synthesis of a model molecule, all-*trans* 3-methyl-nona-2,4,6-trienol **2**.

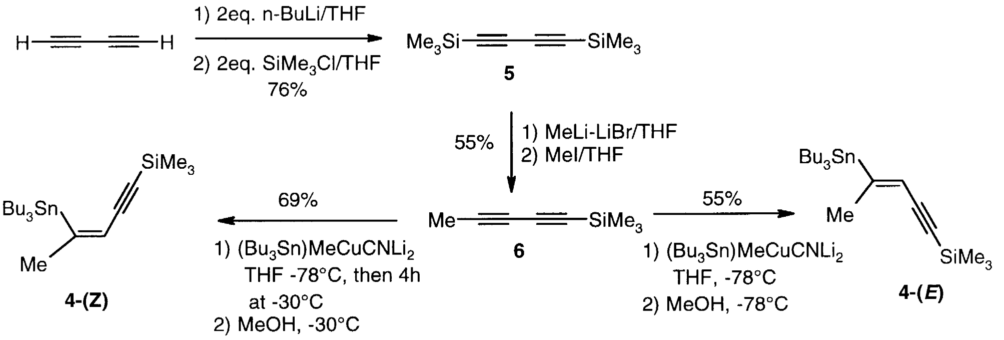
Our retrosynthetic strategy is based on the reductive elimination of the 1,6-dibenzoates **3**, obtained by condensation of the appropriate aldehydes with the enylstannane **4**. The (*Z*)-enyne will be prepared stereoselectively by hydrostannylation of the silyldiyne **5** with a stannylcuprate (Scheme 2).



Scheme 2.

Stannylcupration of alkynes is widely used for the preparation of vinylstannanes.[6] These reactions, as well as the reactions of alkyl-[7] and silylcuprates[8] with terminal alkynes, generally proceed with high regio- and stereoselectivity.

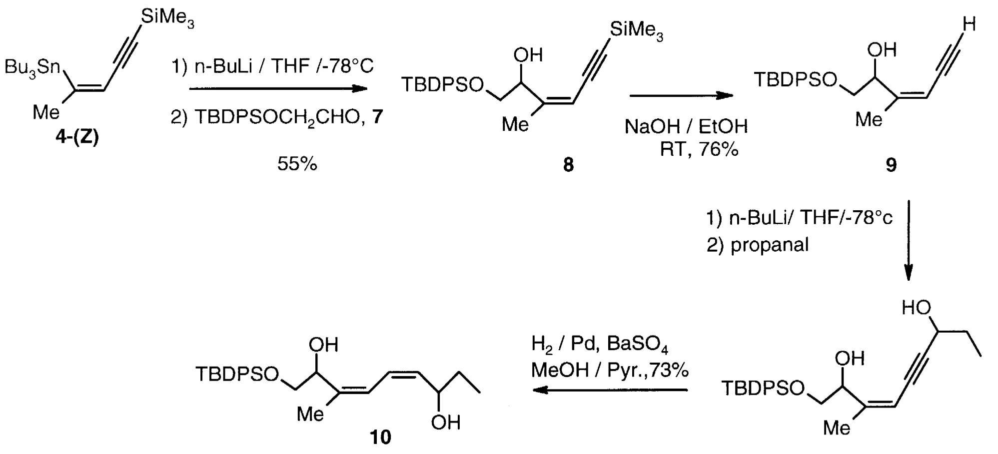
Condensation of lithiated diacetylene with trimethylsilyl chloride afforded bistrimethylsilylbutadiyne **5** which was monolithiated with a methyllithium–lithium bromide complex in THF at room temperature in quantitative yield and reacted with methyl iodide to give trimethylsilylpentadiyne **6** in good yield.[9] Hydrostannylation of the silyldiyne **6** with stannylcyanocuprate $(Bu_3Sn)MeCuCNLi_2$ led to the stereoselective formation of (*E*)- or (*Z*)-stannylenyne **4** according to the experimental conditions: we found that the reaction of **6** with $(Bu_3Sn)MeCuCNLi_2$ in THF at −78°C followed by warming to −30°C during 4 h and methanolysis gave **4**-(*Z*) in 69%; and that **4**-(*E*) was obtained by methanolysis after only 1 h at −78°C (Scheme 3).



Scheme 3.

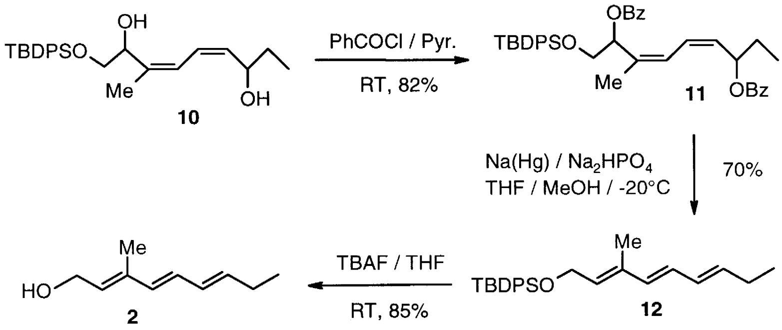
After transmetallation of **4**-(*Z*) (*n*-Buli,THF, −78°C), the vinyl lithium species was added to the protected α-hydroxy aldehyde **7** (prepared by monoprotection of ethylene glycol with sodium hydride and *t*-butyldiphenylsilyl chloride in 95% yield followed by Dess–Martin oxidation[10] in 84% yield). In the resulting enynol **8** the trimethylsilyl protecting group was cleaved to give enyne **9** in 76% yield (20% of the *trans*-silylation product from the primary to the secondary OH was also isolated after chromatographic separation). Condensation of the lithium derivative of **9** with propanal followed by catalytic Lindlar hydrogenation afforded the diene-diol **10**-(*Z*,*Z*) in 62% overall yield (Scheme 4).

The diene-diol **10** was then converted to the dibenzoate **11** using standard conditions (2 equiv. PhCOCl, pyridine, 82%). Reductive elimination of the dibenzoate **11** with 6% Na(Hg)[11] in THF:MeOH



Scheme 4.

(3:1) gave the protected all-*trans* 3-methyl-nona-2,4,6-triene-1-ol **12** in 70% yield. Cleavage of the *t*-butyldiphenylsilyl group with TBAF afforded the all-*trans* product **2** (Scheme 5).



Scheme 5.

The all-*trans* configuration of the triene **2** was assigned by ^{1}H NMR spectroscopy in the presence of a stoichiometric amount of Pr(Fod)$_3$ to separate all the vinylic proton signals. The coupling constants J_{3-4}=J_{5-6}=15 Hz were determined attesting the *E* configuration for the C_{3-4} and C_{5-6} double bonds. The *E* geometry for the C_{1-2} trisubstituted double bond was established using NOE difference experiments.

In conclusion, we have shown that our method for stereospecific synthesis of dienes, trienes and tetraenes was also efficient for the synthesis of methyl substituted trienes. We are currently investigating synthetic applications as well as continuing new syntheses of various substituted polyene fragments.

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