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Regio- and Stereospecificity in Radical Cascade Cyclizations of TMS-Alcyne Containing Allyl Bromomethyldimethylsilyl Ethers

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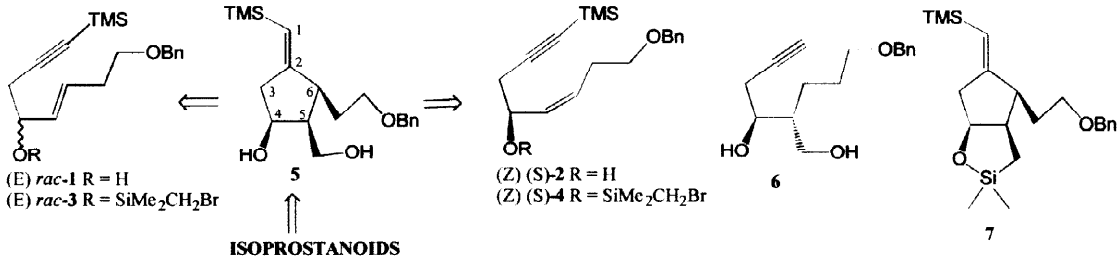
Abstract: Tandem radical cyclization of (E) and (Z) TMS-homopropargyl allyl bromomethyldimethylsilyl ethers is reported to provide an all-*cis* substituted vinylcyclopentanol **5**. Regio- and stereospecificity are discussed.

Up to now, free radical cyclizations have proved to be valuable tools to create carbon-carbon linkages with high control of the regio- and stereoselectivity. An important work has been achieved in this field[1-5] and a very complete review on this topic appeared recently.[6] This communication deals with preliminary results concerning the regio- and stereospecificity of the 5-*exo-trig*, 5-*exo-dig* strategy applied to (E) and (Z) allyl bromomethyldimethylsilyl ethers which contain a trimethylsilyl acetylenic function as the ultimate radical trap; the final target of our strategy is to produce in a concise way the highly functionalized all-*cis* cyclopentanol **5** which will be used as a valuable precursor in the field of isoprostanoids syntheses (scheme 1).



Scheme 1

The starting allyl alcohols (E) *rac*-**1** and (Z) (S)-**2** were synthesized by conventional methods: the racemic (E) isomer **1** was prepared[7] from the Grignard condensation of the trimethylsilyl propargyl bromide with the (E) 5-benzyloxypent-2-enal, whereas the optically active (Z) isomer was obtained as a mixture (Z/E : 85/15) in a eight-steps sequence from (R)-(+)-glycidol. The corresponding bromomethyldimethylsilyl ethers **3** and **4** underwent a radical cascade cyclization ($HSnBu_3$, AIBN, benzene, 80°C) with a high degree of regio- and stereoselectivity. The crude reaction mixture gave after the Tamao oxidation (KF, H_2O_2, DMF, 60°C), the sole cyclic all-*cis* substituted vinylcyclopentanol **5** in moderate yield (*ca.* 30% overall yield after a tedious purification in order to remove tin by-products), together with a lesser amount of the reduced branched

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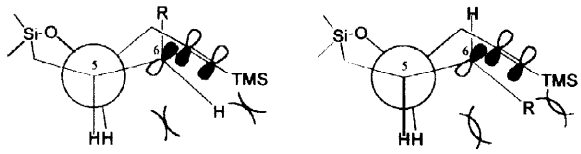
desilylated acyclic diol **6** (10% yield). The first 5-*exo-trig* radical cyclization step provided a mixture of the C-4, C-5 *cis* and *trans* isomers of an intermediate silafuran radical: the *cis* arrangement obviously facilitated the second 5-*exo-dig* cyclization and led to a *cis*-fused bicyclic molecule **7** which after an oxidative cleavage of the C-Si bond, gave the resulting vinylcyclopentanol **5**, in which the *cis* stereochemical relationship between OH and CH_2OH was confirmed by nOe measurements between H_4 and H_5 and the J_{4-5} coupling constant (7.7 Hz); on the contrary, the acyclic *threo* diol **6** originated from the previous *trans* silafuran radical.[8] The relative *cis* configuration at the C-5 and C-6 chiral centers of **5** was successfully assessed by extensive ^{1}H-nmr studies (decoupling and nOe experiments) (J_{5-6} = 9.4 Hz) and the stereochemistry of the double bond of **5** proved to be (E) and was uncontaminated by any (Z) isomer. The observed regiospecificity (no 6-*endo-dig* cyclization detected) was consistent with the whole literature results on 5-hexyn-1-yl radical cyclizations which showed that 5-*exo-dig* process was mainly favoured, although some scarce exceptions[9-11] have been reported. We noticed that the TMS group influenced dramatically the regioselectivity of the cyclization (5-*exo-dig vs.* 6-*endo-dig*) which was not only explained on the grounds of electronic factors, but mainly by the steric hindrance[9] created on the acetylenic unit end which prevented the approach of the incoming secondary radical-centered carbon. The stereospecific formation of the strained diastereomer **5** during the second 5-*exo-dig* cyclization step could account for an early transition state model **A** (scheme 2) in which steric interactions were minimized between H_6 and both the TMS group and H_5; on the other hand, the disfavoured model **B** exhibited more severe constraints involving the benzyloxyethyl chain. Finally, in agreement with the literature,[6] the geometry (E) or (Z) of the starting allyl ethers **3** and **4** did not interfere with the regioselectivity and stereoselectivity of the radical cascade cyclization.



A **B**

Scheme 2 - R= CH_2CH_2OBn

This work has illustrated for the first time, that a consecutive tandem 5-*exo-trig*, 5-*exo-dig* radical cyclization applied to a chiral acyclic TMS-homopropargyl allyl bromomethyldimethylsilyl ether, was able to generate stereospecifically an all-*cis* trisubstituted vinylcyclopentanol. The use of this suitable intermediate is under progress for the construction of the isoprostanoids framework.

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