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Selective Termination of a Polyene Cyclization by an Internally Situated Allylsilane Group

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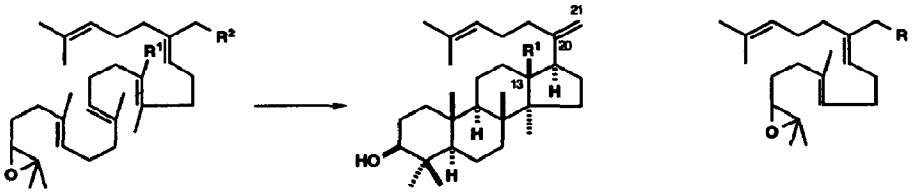
Abstract: The cyclization of epoxides **6** and **7**, incorporating the internally situated propenyl and allylsilane terminator groups respectively, has demonstrated that the allylsilane function is the far superior group for terminating the cyclization process, and does so in a highly efficient and selective manner. Thus, treatment of **6** with (*i*-PrO)$TiCl_3$ afforded bicyclic alcohols **23** in 79-82% yield.

Biomimetic polyene cyclizations have been successfully applied to the construction of natural products, particularly steroids and polycyclic triterpenoids.[1] However, these synthetic cyclization substrates have generally only a passing resemblance to 2,3-oxidosqualene (**1**), the enzymatic precursor to these natural products.[2] The acid-catalyzed cyclization of **1** leads to just two tricyclic products, a result that has substantially limited the use of **1** as a substrate for nonenzymic cyclization studies.[3] By appropriate functionalization of **1** it may prove possible to design oxidosqualene derivatives which could potentially undergo nonenzymic cyclization to furnish predictable polycyclic materials that closely resemble the enzymatic (natural) products. Thus it was our aim to design suitably functionalized polyene substrates which, upon acid-promoted reaction, would give direct access to the tetracyclic triterpenoid dammaradienol (**2**).[4]



1: R^1 = H, R^2 = H
3: R^1 = F, R^2 = H
4: R^1 = F, R^2 = $SiMe_3$

2: R^1 = H
5: R^1 = F

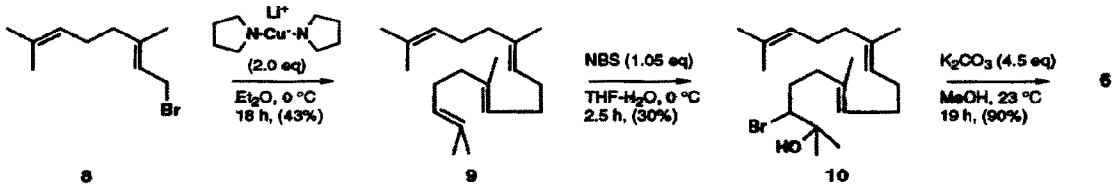
6: R = H
7: R = $SiMe_3$

(1)

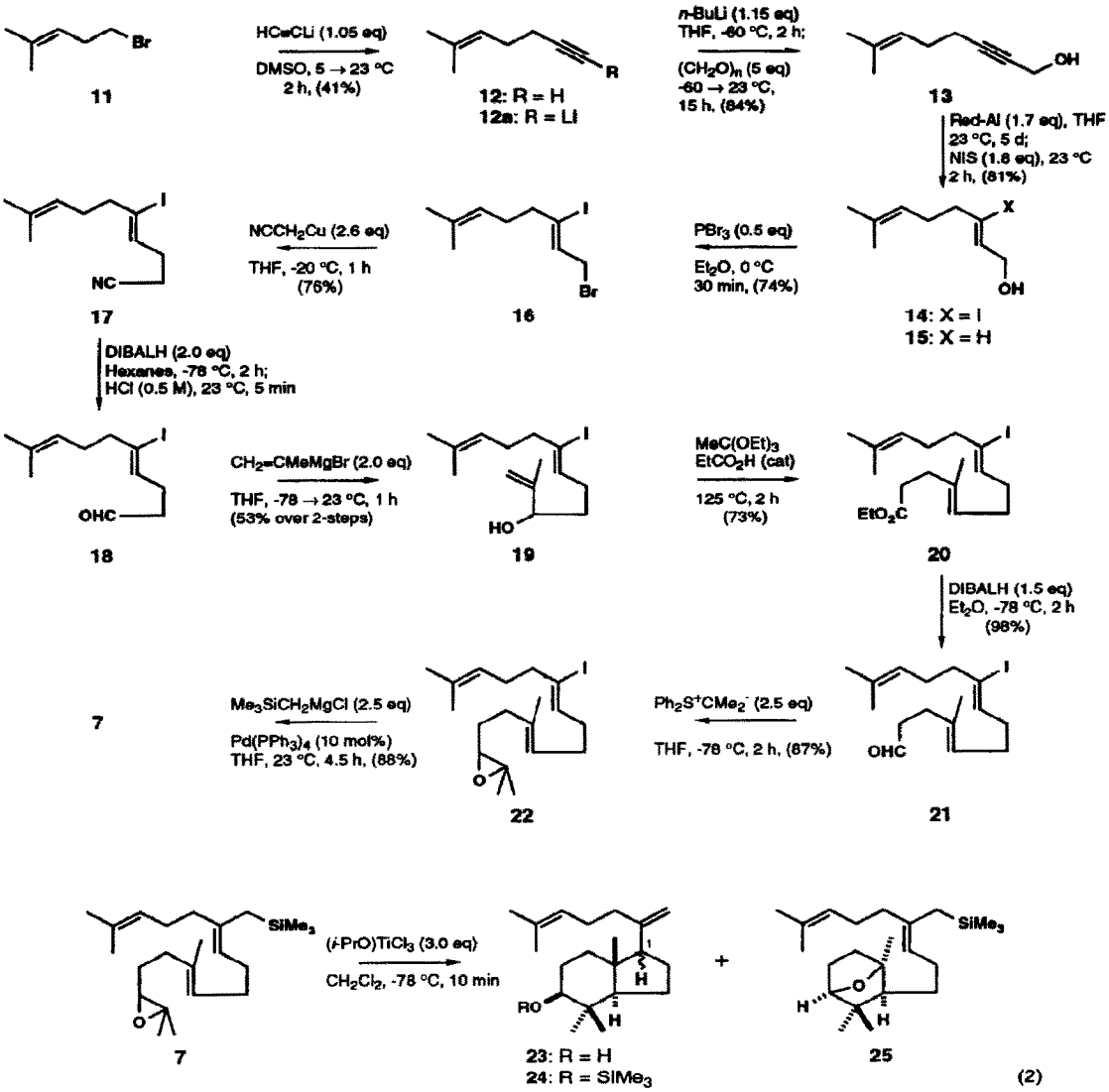
Two fluorooxidosqualene derivatives **3** and **4** were selected as candidate substrates. Cyclization of either polyene could potentially furnish fluorotetracycle **5**,[5,6] and subsequent stereoselective reduction of the β-C13 fluorine atom, with retention of configuration,[7] would provide **2** (eq 1). The anticipated stereoselective synthesis of **3** and especially **4** was not trivial and so two model epoxides **6** and **7** were prepared in order to predict the cyclization behavior of the CD rings of **3** and **4**.

Epoxide-initiated cationic cyclizations have proven to be capricious and yields of fully cyclized products have been low,[8] however, recent studies have demonstrated that judicious choice of the acid used to promote the cyclization can furnish two or three rings in good yield.[9] The selective termination of the cyclization would require regioselective α-elimination of R from *pro*-C21' (**II**) to create the C20'-21' alkene **III**. Simple proton elimination (**6**→ **II**:R=H→ **III**) may not be sufficiently selective because cations like **II** have a susceptibility to undergo backbone rearrangements.[3,10] Allylsilanes have proven to be effective terminators of polyene cyclizations when appended at the terminus of the polyene substrate[11] and could potentially selectively terminate

Scheme 1:

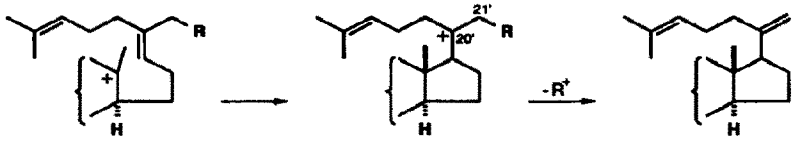


Scheme 2:



(2)

the cyclization when situated internally along the polyene backbone (7→ II:R=$SiMe_3$→ III). Although much simpler than **3** and **4**, it was expected that **6** and **7** would provide valuable empirical data on the ability of the two groups -CH_3 and -CH_2SiMe_3 located at *pro*-C20' to influence the 5-membered D ring formation and to terminate the polyene cascade.



I II III

2,3-Oxidodigeranyl (**6**) was synthesized from digeranyl (**9**)[12] by regioselective terminal bromohydrin formation with NBS in THF-H_2O to **10**, and then treatment of **10** with methanolic K_2CO_3 (Scheme 1).[13] The preparation of substrate **7** was more challenging as it required the stereospecific construction of the (*Z*)-trisubstituted allylsilane moiety (Scheme 2).[13] Thus, alkylation of lithium acetylide with 1-bromo-4-methyl-3-pentene (**11**) gave enyne **12**[14] which was converted to the propargylic alcohol **13** by deprotonation with *n*-BuLi, to generate the lithium acetylide **12a**[14], and reaction with paraformaldehyde. Reduction of **13** with Red-Al followed by reaction with *N*-iodosuccimide[15] gave predominantly 3-iodo (*Z*)-allylic alcohol **14**, along with (*E*)-allylic alcohol **15** and the position isomeric 2-iodo alcohol (ratio, 20:2:1 respectively); distillation separated **14** in 81% yield. The reduction-iodination of **13** with Red-Al-NIS proved to be more selective for **14** than with $LiAlH_4$/NaOMe-I_2 (ratio, 9:3:2).[16] Bromination of **14** with PBr_3 gave **16** which upon reaction with cyanomethylcopper[17] afforded nitrile **17** and then reduction with DIBALH gave aldehyde **18**. Reaction of **18** with CH_2=C(Me)MgBr gave alcohol **19** which underwent orthoester Claisen rearrangement[18] to ester **20** with high *trans* stereoselectivity (97:3). Reduction of **20** with DIBALH, and alkylation of the resulting aldehyde **21**, with the sulfur ylide derived from $Ph_2SCHMe_2^+BF_4^-$,[19] gave epoxide **22**. The palladium-catalyzed coupling of epoxy iodide **22** with Me_3SiCH_2MgCl gave epoxy allylsilane **7**.[20]

Cyclization of epoxide **6** with (2-propoxy)titanium trichloride[9e] (3.0 eq) in CH_2Cl_2 at -78 °C for 10 min gave a complex mixture of components [GC ratio: 13:15:12:11:6:8 (%) as the major products, plus 11 minor products (1-5%)], and none of the major products were consistent with the desired bicyclic alcohol **23**. In contrast, cyclization of epoxide **7** with (*i*-PrO)$TiCl_3$ (3.0 eq, CH_2Cl_2, -78 °C, 10 min), followed by basic aqueous work-up ($NaHCO_3$) and chromatography, afforded bicyclic alcohols **23** (60%), bicyclic TMS ethers **24** (23%), and bicyclic ether **25** (6%) (eq 2).[13] Both **23** and **24** were formed as a mixture of the C1α and C1β epimers (1:1, 1:1, respectively) (indene numbering).[21] Exposure of TMS ethers **24** to aqueous HCl in THF gave alcohols **23** (94%). Hence the overall isolated yield of alcohols **23** from **7** was 82%. Cyclization of **7** with (*i*-PrO)$TiCl_3$ (as above) followed by treatment with aqueous acid (HCl) directly furnished the bicyclic alcohols **23** (1:1) in 79% isolated yield. The cyclization of **7** was highly selective for the formation of the trans-fused A/B ring junction giving rise to only two bicyclic products **23**. The formation of an epimeric mixture at the center equivalent to C1 is commonly observed when attempting to create a 5-membered ring by a cationic polyene cyclization.[1,11] There were no other major products observed resulting from either cationic backbone rearrangement or involvement of the terminal olefin in the cyclization cascade.

In conclusion, methodology for the stereoselective construction of functionalized trisubstituted (*Z*)-allylsilanes has been developed. The cyclization of epoxides **6** and **7** has demonstrated that the internally situated allylsilane function is the far superior group for selectively terminating the cyclization process. In addition, the yield of the cyclization **7**→ **23**, 79-82%, is very respectable for an epoxide-initiated process.[22]

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22. Correspondence regarding this Letter should be addressed to W. S. Johnson, Stanford University.

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