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The Tetramethylallyl Cation as a Surrogate for the Epoxide Function as an Initiator of Biomimetic Polyene Pentacyclizations. Total Synthesis of Sophoradiol.

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Abstract: The tetramethylallyl cation has proven to be an effective substitute for the epoxide as an initiator for biomimetic polyene cyclizations. This methodology was applied to the total synthesis of the pentacyclic triterpenoid sophoradiol (1) whereby the key step of the strategy involved the protic acid-catalyzed pentacyclization of tetramethylallyl alcohol 9 which furnished fluoropentacycle 11 as the major product in 31 % yield. Lewis acid-catalyzed cyclization of 9 gave the dehydrofluorinated pentacycle 12 in 50 % yield.

Although the tetramethylallyl (TMA) cation function for initiating polyene cyclizations was discovered in 1969[1] there have since been very few further examples[2] of its use in place of the epoxide group (see Fig. 1), despite the fact that the former function promises to give significantly higher cyclization yields than the latter. The major reason for the neglect of the TMA cation method is probably due to difficulties in synthesizing the required cyclization substrates in good yield. This matter has now been largely resolved and the TMA cation initiation has been compared directly with the epoxide case in a *pentacyclization*, the isolated yield for the cyclization step of the former being at least a three-fold increase over that of the latter. The details of this study are the subject of the present communication which also discloses its application to the total synthesis of sophoradiol (1), a pentacyclic triterpenoid with interesting biological properties.[3,4]

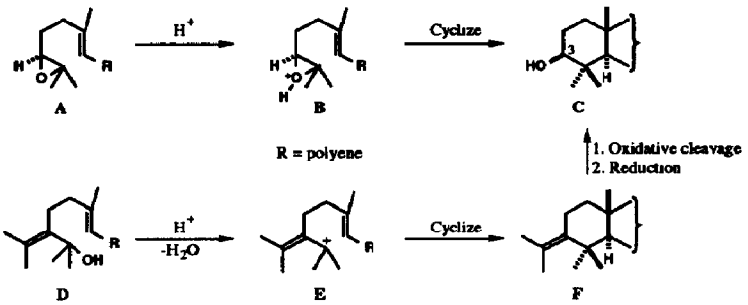
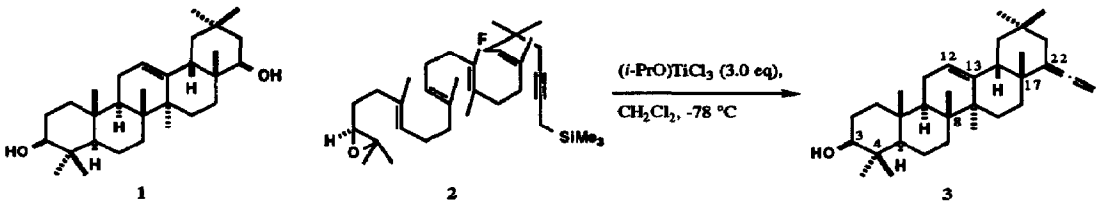


Figure 1. Comparison of epoxide and TMA cation initiated cyclizations.

Our previous studies showed that the epoxide-initiated pentacyclization of polyene **2** furnished a relatively complex mixture from which pentacycle **3** was isolated in 10 % yield (GC yield: 21 %).[5] This was a significant result when compared to the acid-catalyzed cyclization of oxidosqualene[6] and other previous cyclization studies,[7] but was impractical with regard to an application to the synthesis of pentacyclic triterpenoids. An alternative to the epoxide-initiator was required which would prove to be an effective polyene

cyclization initiator, and then be readily degraded to yield the necessary A-ring functionality. Therefore we decided to explore, as a surrogate initiator, the TMA cation that would be generated by the acid treatment of the corresponding TMA alcohol **9**.



1 **2** **3**

The intimate relationship between these two initiators is outlined in figure 1. Tetramethylallylic alcohol **D** on treatment with acid generates the symmetrical TMA cation **E** which in turn undergoes cyclization **E**→**F**. Degradation of the resulting isopropylidenyl group in the cyclization product **F** was expected to yield the C3-β-OH. The overall conversion **D**→**F**→**C** would be equivalent to the epoxide-initiated process, **A**→**C**.

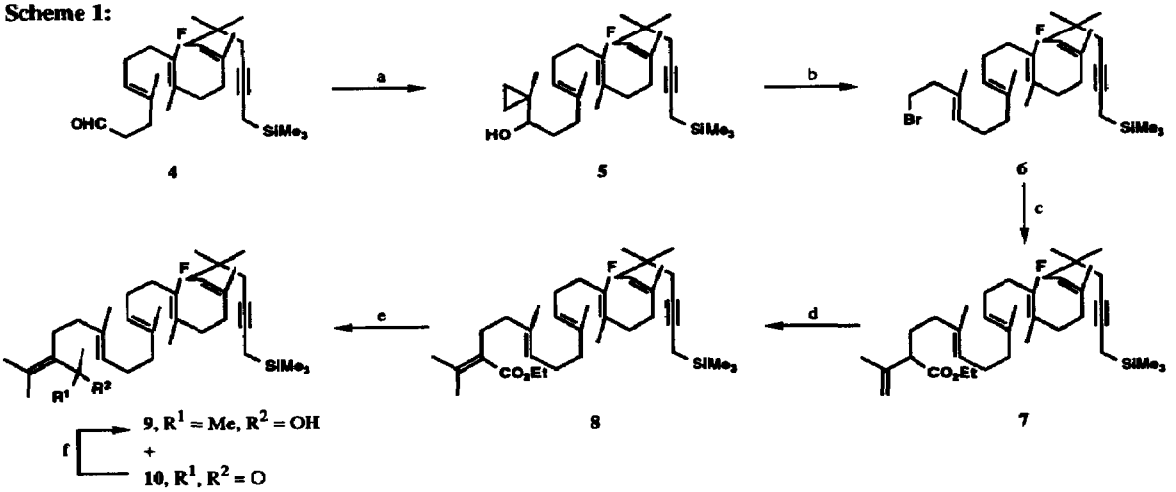
The synthesis of the cyclization substrate, **9**, was performed according to the procedure outlined in Scheme 1.[8] The advanced trienyne aldehyde intermediate **4**, incorporating the *trans*-alkene at *pro*-C8, the *trans*-fluoroalkene at *pro*-C13, the *cis*-alkene at *pro*-C17, and the propargyl silane terminator, has been synthesized previously (23 steps).[5] Thus, reaction of **4** with (1-methyl-1-cyclopropyl)magnesium bromide[9] gave cyclopropyl carbinol **5** which underwent rearrangement with $MgBr_2$ to homoallylic bromide **6** with high *trans*-stereoselectivity (99:1).[10] Alkylation of the lithium enolate of ethyl 3,3-dimethylacrylate[11] with **6** gave the βγ-enoate **7** which was isomerised to the αβ-isomer **8** by treatment with potassium *t*-butoxide. Methylation of **8** with excess methyllithium invariably gave a mixture of predominantly (*E,E,Z,Z*)-alcohol **9** along with ketone **10**. Chromatographic separation of **9** and **10**, and then retreatment of **10** with MeLi also furnished **9**. The conversion **6**→**9** represents a substantial improvement (chemical yields, milder conditions, fewer steps) over previously reported procedures.[1, 2]

Cyclization of **9** under protic acid conditions with trifluoroacetic acid (1 % TFA in CH_2Cl_2, -78 °C, 15 min) gave the fluoropentacycle **11** in 31 % isolated yield (Scheme 2).[8] In comparison, treatment of **9** with tin(IV) chloride (3.0 eq, CH_2Cl_2, -78 °C, 10 min), resulted in facile cyclization to afford pentacycle **12** in 50 % isolated yield. Fluoropentacycle **11** was not isolated in this case, but evidently underwent regioselective *in situ* dehydrofluorination to generate the C12-13 olefinic bond.[4e, 5] Hence, the TMA cation initiator allows for a substantial increase in the the yield of pentacyclic products in the cyclization step and since the conversion equivalent to **F**→**C** (Fig. 1) proved to be highly efficient (see below) the surrogate approach is very successful.

The cyclization product **11** is suitably functionalized at C3, C13 and C22 to allow conversion to **1** with a minimum of synthetic manipulations.[12] Simultaneous oxidative cleavage of the C3 isopropylidene and C22 vinylidene groups of **11** with catalytic $RuCl_3$ and $NaIO_4$[13] furnished the diketone **13** (Scheme 3)[8] which then underwent regiospecific dehydrofluorination (C12-13) to yield the enedione **14** when treated with $SnCl_4$. Stereoselective reduction of **14** with DIBAL gave predominantly (±)-sophoradiol (**1**) along with olean-12-ene-3β,22α-diol[14] (87 %, ratio 4.1:1) which were separable by recrystallization. Synthetic (±)-sophoradiol (**1**), mp 234-236 °C, was unequivocally identified with an authentic sample of natural (+)-**1**.[15] As a natural extension of this study, sophoradiol (**1**) was converted to olean-12-ene (**15**)[16, 17] by conversion to the bis-methyl xanthate and then reduction with *n*-Bu_3SnH.[4e]

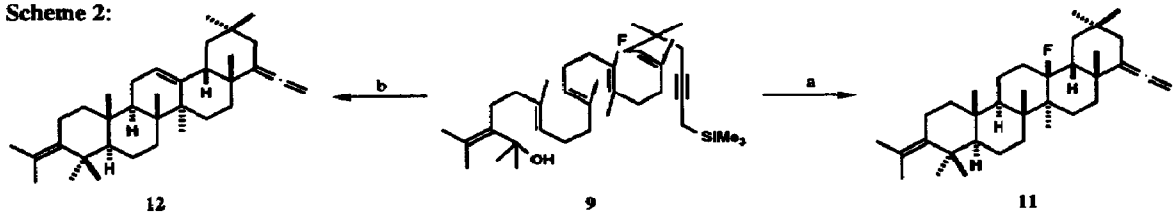
In conclusion, we have demonstrated that the tetramethylallyl cation is an effective substitute to the epoxide as an initiator for biomimetic polyene pentacyclizations and that such cyclizations represent a viable strategy for the total synthesis of pentacyclic triterpenoids. This methodology has been applied to the total synthesis of the oleananes sophoradiol (**1**) and olean-12-ene (**15**). In addition, the $SnCl_4$ promoted cyclization of **9** to **12** is the highest recorded yield (50 %), to date, for a pentacyclization.

Scheme 1:



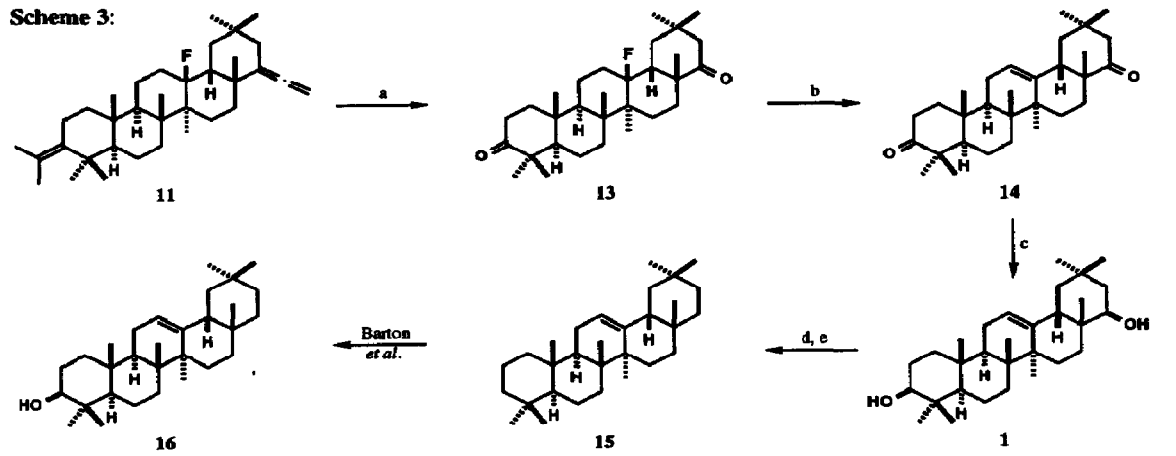
Reagents and conditions: (a), (1-Methyl-1-cyclopropyl)magnesium bromide (3.0 eq), THF, -78 °C then 23 °C, 1.6 h, 55 %; (b), $MgBr_2(Et_2O)_2$ (5.0 eq), Et_2O, reflux, 70 h, 69 %; (c), $Me_2C{=}CHCO_2Et$ (2.6 eq), LiN-*i*-Pr_2 (2.5 eq), HMPA (4.0 eq), THF, -78 °C, 30 min, add **6**, -78 °C, 20 min then 0 °C, 4 h, 93 %; (d), *t*-BuOK (1.0 eq), THF, 0 °C, 30 min, **8**:**7**, 91:9, 74 %; (e), MeLi (5.0 eq), Et_2O, 23 °C, 30 min, **9**, 68 %, **10**, 21 %; (f), MeLi (3.0 eq), Et_2O, 23 °C, 30 min, 44 % (52 % based on recovered **10**).

Scheme 2:



Reagents and conditions: (a), 1 % CF_3CO_2H-CH_2Cl_2, -78 °C, 15 min, 31 %; (b), $SnCl_4$ (3.0 eq), CH_2Cl_2, -78 °C, 10 min, 50 %.

Scheme 3:



Reagents and conditions: (a), $RuCl_3$ (cat.), $NaIO_4$ (10 eq), MeCN-CCl_4-H_2O, 23 °C, 15 h, 88 %; (b), $SnCl_4$ (2.0 eq), CH_2Cl_2, -15 °C, 1 h, 92 %; (c), DIBAL (5 eq), Et_2O, 23 °C, 30 min, 3β,22β:3β,22α, 4:1, 87 %; (d), *n*-BuLi (5 eq), THF, 0 °C, 45 min, CS_2 (10 eq), 23 °C, 4 h, add MeI (10 eq), 23 °C, 18 h; (e), *n*-Bu_3SnH (2.75 eq), AIBN (cat.), PhMe, reflux, 1 h, 31 % over 2 steps.

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3. Sophoradiol (**1**) has been isolated from *Abrus cantoniensis* HANCE (3a) and other plant sources (3b). This herb has long been used in south China and southeast Asia as a folk medicine for the treatment of infectious hepatitis, and the herb's efficiency towards this disease has been substantiated by clinical trials (3c). Identification of the active components is under investigation (3c). In addition, **1** exhibits cytotoxicity against human cancer cell lines (3d). (a), Mak, T. C. W.; Chiang, T.-C.; Chang, H.-M. *J. Chem. Soc., Chem. Commun.* **1982**, 785-786; (b), Kinjo, J.; Matsumoto, K.; Inoue, M.; Takeshita, T.; Nohara, T. *Chem. Pharm. Bull.* **1991**, *39*, 116-119, and references therein; (c), Chiang, T.-C.; Chang, H.-M. *Planta Med.* **1982**, *46*, 52-55, and references therein; (d), Ling, H. C.; King, M. L.; Chen, C. F.; Hsu, K. P.; Su, M. H.; Lin, M. H. *Chung-hua I Hsueh Tsa Chih* **1982**, *29*, 308-315, (see: *Chem. Abs.* **1983**, *97*, 120120p).
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17. The synthesis of olean-12-ene (**15**) also constitutes a formal total synthesis of β-amyrin (**16**) as **15** was an intermediate in Barton's synthesis of **16** (ref. 4a).

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