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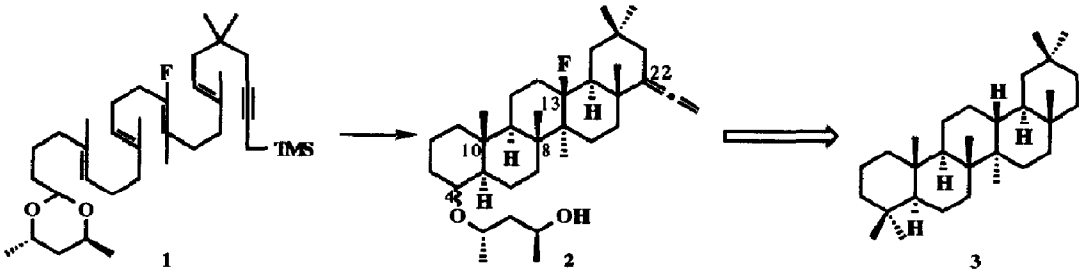
Towards Oleananes: Geminal Dimethylation at C-4

Garth S. Jones[1]

Department of Chemistry, Stanford University, Stanford, CA, 94305, USA

Abstract: A model of the ABC rings of the oleananes, prepared by biomimetic polyene cyclization, shows that the system is sufficiently rigid to prevent epimerization of the C-5 hydrogen with a ketone functionality in place at C-4. Such a sterically hindered ketone has been successfully transformed to a geminal dimethyl group by a three-step procedure.

As a continuation of our investigation into the biomimetic synthesis of the pentacyclic triterpenoids such as β-amyrin and its analogues, we are pursuing a total synthesis of 18α(H)-oleanane, **3**. Pentacycle **2**, which may be synthesized by the asymmetric biomimetic polyene cyclization of **1** in good yield,[2] must be modified at three sites to complete the total synthesis. The allene at C-22 must be removed completely, the C-13 fluorine atom reduced stereospecifically, and the acetal fragment at C-4 converted to a geminal dimethyl group. Since prior work has provided methodology to to fulfill the first two requirements,[3] the most problematic of the three is the conversion of the acetal remnant to the C-4 geminal dimethyl group. Creating quaternary centers at sterically hindered sites has proved to be a general problem with the acetal-inititated biomimetic polyene cyclization based syntheses, thus we are very interested in identifying a general solution.



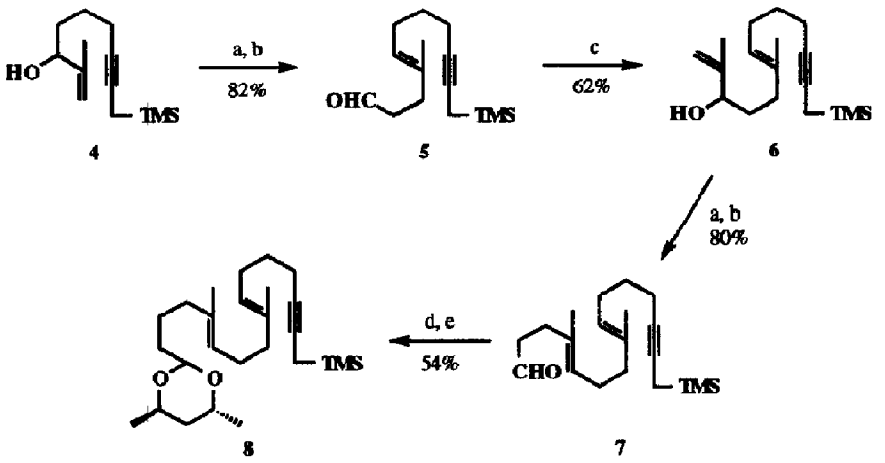
The acetal fragment may be removed by well-established methodology,[3] leaving epimeric C-4 alcohols that may, in turn, be oxidized to a ketone functionality. To our knowledge the direct geminal dimethylation of such a hindered site on a polycyclic triterpenoid or steroid has not been investigated. Several approaches based on organometallic reagents for the direct geminal dimethylation of ketones have been developed.[4] These methods generally require either sterically unhindered or benzylic ketones to be successful. Herein we report our efforts to investigate this problem with a tricyclic model of the ABC rings of oleananes prepared via a biomimetic polyene cyclization.

Initial experiments with the readily available 4-cholestanone[5] proved troublesome on two accounts. First, our attempts to apply methodology developed by Reetz[6] in which ketones may be converted directly to geminal dimethyl groups by reaction with Me_2TiCl_2 resulted in the addition of only one methyl group, which we attribute to the steric congestion at the C-4 center. Much more worrisome, however, was the fact that 4-cholestanone epimerizes readily to give a 2:1 mixture of *trans*:*cis* AB ring junctions. This phenomenon has

been observed in a number of steroidal systems[7] but its prevalence in the corresponding oleananes is unknown.

We theorized that the C-8 methyl group in 18α(H)-oleanane would rigidify the ring system and prevent epimerization from occurring. To probe this issue and methods for the required geminal dimethylation, we prepared a model that contains the key features of rings ABC of oleanane. Substrate **8** includes the critical *pro*-C-8 and *pro*-C-10 methyl groups, as well as the 2,4-pentanediol acetal initiator that was employed in the pentacyclization. The nucleophilic propargylsilane terminator was chosen for its ability to promote biomimetic polyene cyclizations under mild conditions.

Substrate **8** was synthesized from allylic alcohol **4** (Scheme 1).[8,9] Thus, orthoester Claisen rearrangement[10] followed by DIBALH reduction of the resultant ester afforded the *trans* aldehyde **5**. The rearrangement proceeded in good yield and with high *trans*:*cis* selectivity (>99:1). Allylic alcohol **6** was prepared by reaction of **5** with 2-propenylmagnesium bromide. A second orthoester Claisen rearrangement followed again by DIBALH reduction gave aldehyde **7**. As before, the rearrangement resulted in the desired trans olefin as the major product (*trans*:*cis* 96:4). The synthesis was finished by Wittig reaction with (methoxymethyl)triphenylphosphorane followed by acetalization with racemic 2,4-pentanediol.[11]



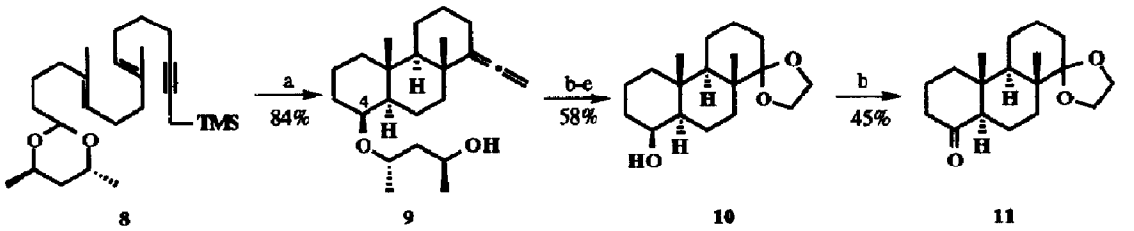
Reagents and Conditions: (a) triethylorthoacetate, butyric acid; (b) DIBALH, Et_2O; (c) 2-propenylmagnesium bromide; (d) Ph_3P=CHOMe, THF; (e) (±)-2,4-pentanediol, pTSA, benzene.

Scheme 1.

Acetal **8** was cyclized by treatment with $SnCl_4$ (3 equiv, -40°C, 30 min) to give tricycle **9** in 84% yield as a crystalline solid (Scheme 2).[12] By analysis of the NMR spectra and correlation of the data with similar systems it is clear that the product is the expected C-4 β-alkoxy, all-*trans* compound. From the standpoint of the cyclization, this is an interesting result, since few biomimetic cyclizations proceed in such high yields without the formation of mixtures of side products. In contrast to previous results,[13] the presence of an unsubstituted, six-membered *pro*-C ring bearing the propargylsilane terminator did not lead to a mixture of *trans* and *cis* ring fusions at the BC ring junction.

The ketal fragment was removed by PCC oxidation followed by base-catalyzed β-elimination in nearly quantitative yield. Ozonolysis cleaved the allene functionality in C-4 alcohol **10** and the resultant ketone ketalized with ethylene glycol. The C-4 alcohol was then oxidized with PCC to afford the corresponding ketone. As we had predicted, C-4 ketone **11** did not epimerize under standard work-up conditions. Compared

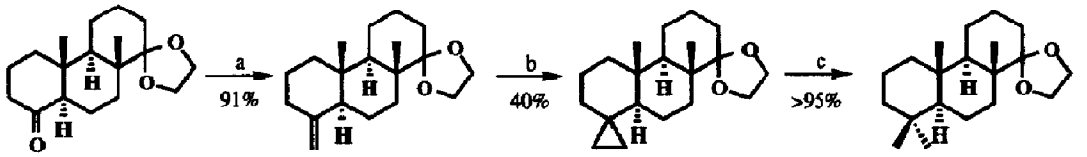
to the analogous steroidal systems, the axial methyls on adjacent ring junctures appear to rigidify the system and prevent the folding required for a *cis* A-B ring arrangement.



Reagents and Conditions: (a) 3 equiv $SnCl_4$, CH_2Cl_2, -40°C, 30 min; (b) PCC, NaOAc, CH_2Cl_2, powdered 4A MS; (c) KOH, THF, MeOH, 60 °C, 18 h; (d) O_3, CH_2Cl_2, MeOH, -78 °C, then Me_2S; (e) ethylene glycol, pTSA, benzene.

Scheme 2.

Since Me_2TiCl_2 did not appear promising for the introduction of the C-4 dimethyl group, we adopted a more traditional three-step approach (Scheme 3).[14] Wittig reaction with methylenetriphenylphosphorane afforded the exo-olefin **12** in good yield. Modified Simmons-Smith conditions (Et_2Zn, CH_2I_2)[15] resulted in the formation of spirocyclopropane **13**. The cyclopropane was opened regiospecifically to give the desired geminal dimethyl group by hydrogenation over PtO_2.



Reagents and Conditions: (a) $Ph_3P{=}CH_2$, THF, -78 to -40 °C; (b) Et_2Zn, CH_2I_2, toluene, 55 °C, 18 h; (c) 1 atm. H_2, PtO_2, AcOH, 18 h.

Scheme 3.

With the above study complete, the way appears clear for a successful synthesis of 18α(H)-oleanane and a series of analogous compounds. The three-step procedure proceeds smoothly in spite of the steric hindrance at C-4. Furthermore, the presence of the C-10 methyl appears to restrict the system's flexibility to the point that the C-4 ketone does not epimerize. Finally, the successful cyclization of substrate **7** demonstrates that with a careful choice of initiator and terminator such polyenes may be cyclized with a high degree of specificity under mild conditions.

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11. Data for ketal **32**: IR (film) ν 2900, 1430, 1365, 1235, 1175, 1165, 840 cm^{-1}; ^1H NMR δ 5.07 (m, 2 H), 4.81 (t, J = 4.8 Hz, 1 H), 4.27 (t, J = 6.4 Hz, 1 H), 3.91 (dd, J = 5.9, 2.2 Hz, 1 H), 2.11 (m, 2 H), 2.04 (m, 4 H), 1.94 (m, 4 H), 1.58 (s, 3 H), 1.56 (s, 3 H), 1.20-1.55 (m, 8 H), 1.32 (d, J = 6.8 Hz, 3 H), 1.17 (d, J = 6.2 Hz, 3 H), 0.07 (s, 9 H); ^{13}C NMR δ 134.8, 124.5, 123.8, 94.3, 78.8, 77.4, 67.9, 67.4, 39.8, 39.5, 36.8, 34.9, 29.6, 27.1, 26.6, 22.5, 21.9, 18.5, 17.2, 15.8, 6.9, -2.1; Anal. calcd for $C_{26}H_{46}O_2Si$: C, 74.58; H, 11.07. Found: C, 74.56; H, 11.25.
12. **Cyclization of Substrate 32.** Substrate **32** (0.327 g, 0.79 mmol) was dissolved in CH_2Cl_2 (10 mL), cooled to -40 °C (CH_3CN/CO_2 bath) and treated with $SnCl_4$ (2.4 mL of a 1.0 M solution in CH_2Cl_2,3 equiv). The mixture was allowed to warm to -20 °C over 40 min and then the reaction was quenched with 25% Et_3N:MeOH (5 mL). The mixture was diluted with CH_2Cl_2 (20 mL) and washed with 10% HCl (25 mL), saturated $NaHCO_3$ (20 mL), and brine (20 mL). The solution was dried, concentrated, and the residue purified by MPLC (30 cm column, sg, 2.5-5% EtOAc:hexanes as eluant) to yield the product, which crystallized on standing (0.229 g, 84%). Powder; ^1H NMR δ 4.59 (m, 1 H), 4.55 (m, 1 H), 4.15 (m, 1 H), 3.72 (m, 1 H), 3.51 (s, 1 H), 3.44 (m, 1 H), 2.20 (m, 1 H), 2.05 (m, 1 H), 1.10-1.90 (m, 16 H), 1.14 (s, 3 H), 1.01 (s, 3 H); ^{13}C NMR δ 201.6, 113.7, 77.1, 74.7, 71.0, 64.2, 57.4, 50.7, 44.7, 39.6, 39.1, 37.3, 37.1, 29.3, 28.1, 27.8, 23.9, 23.6, 21.1, 20.4, 18.2, 17.2, 16.1; Anal. calcd for $C_{23}H_{38}O_2$: C, 79.71; H, 11.05. Found: C, 79.58; H, 10.70.
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