A New Strategy for Stereocontrol of Cation−Olefin Cyclization. The First Chemical Emulation of the A/B-*trans*-9,10-*syn*-Folding Pathway of Steroid Biosynthesis from 2,3-Oxidosqualene

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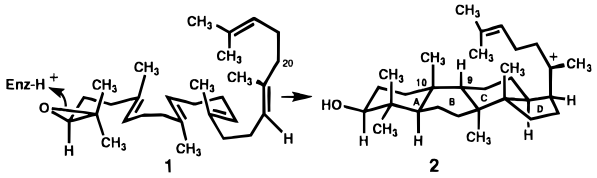
The enzymic cyclization of (*S*)-2,3-oxidosqualene (**1**) to the protosterol cation (**2**)[1,2] has never been emulated in a chemical system, in part because the A/B-*trans*, 9,10-*syn*, B/C-*trans* stereochemistry of **2**, which requires boat geometry for the B ring, is several kcal/mol less stable than the alternative *trans-anti-trans* A/B/C arrangement. In general, chemically conducted



cation−olefin cyclizations have led to *trans-anti-trans* type fused ring systems (triterpene folding) exclusively.[1a,3] We report herein on a substrate design which favors cyclization to A/B-*trans*, 9,10-*syn* product (steroid numbering) and which suggests a new approach to the control of stereochemistry and olefinic face selectivity in cation−olefin cyclizations.

The specific substrate that was the focus of this investigation was the chiral oxirane **4**, which was synthesized as a 1:1 mixture of *E*- and *Z*-isomers[4,5] at the vinyl trifluoroethyl ether subunit by Wittig olefination of the corresponding ketone (**3**) (Ph_3P^+-$CH_2OCH_2CF_3$ Br^-, potassium *tert*-amyl oxide, C_7H_8, 25 °C, 4.5 h). Treatment of the 1:1 mixture of *E*- and *Z*-**4** with $MeAlCl_2$ (2 equiv) in CH_2Cl_2 at −95 °C for 1 h produced a single tetracyclic hydroxy α,β-enone (**5**) which was obtained pure in 40% yield after flash column chromatography on silica gel. The structure of **5** was determined unambiguously as described below.[6] It is likely that **5** arises from the *E*-form of **4** because of the correspondence of vinyl ether geometry. It may also be that tetracyclic products are not formed from the *Z*-form of **4** because such structures would be severely destabilized by steric repulsion between C(15) of the D-ring and the trifluoroethoxy group. On the basis of this assumption, the yield of the cyclization product would be 80%.

The oily cyclization product **5** was converted to the crystalline tetracyclic ketone bis-silyl ether **7**, mp 145.5−146 °C, by the following sequence: (1) silylation of the 3-hydroxyl group (1.3 equiv of *tert*-butyldimethylsilyl triflate, TBSOTf, and 2.3 equiv of 2,6-lutidine in THF at −78 °C for 1 h), (2) selective hydrogenation of the 14,15-double bond (H_2, Pd−C, EtOH, 25 °C, 3 h), (3) oxidative cleavage of the C(7) exocyclic vinyl ether to form **6** (0.05 equiv of $RuCl_3$, 4 equiv of $NaIO_4$ in CCl_4−CH_3CN−H_2O at 25 °C for 1.5 h), and (4) transformation of ketone **6** to the enol ether **7** (1.3 equiv of TBSOTf and 2 equiv of KHMDS in THF at −78 °C for 45 min).

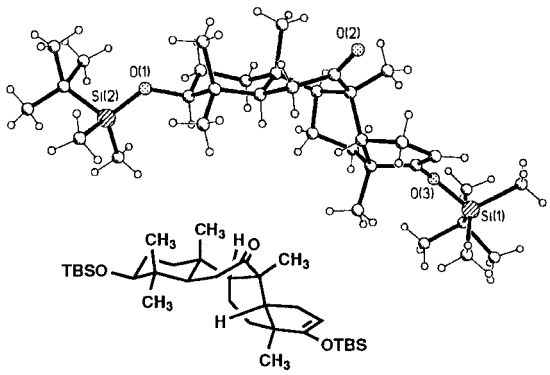
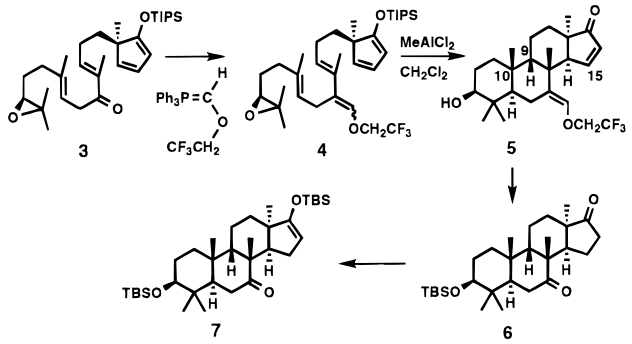
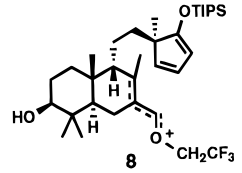


Figure 1. X-ray crystal structure of TBS-enol ether 7.



A crystal of **7** was subjected to X-ray crystallographic analysis which revealed the three-dimensional structure shown in Figure 1.[7] The structure of **7** involves the *syn*-relationship between the H at C(9) and the CH_3 at C(10) and A/B-*trans* geometry in common with the protosterol system. The formation of **7** therefore must involve the same olefinic face selectivity (i.e., substrate folding) which is involved in forming the A- and B-rings during sterol biosynthesis. To the best of our knowledge this is the first time that this stereochemical pathway has been demonstrated for a non-enzymic cation−olefin cyclization. The *cis*-fusion of the B- and C-rings, which provides a clear indication that C-ring formation is not concerted with B-ring closure, reflects the preferred face selectivity for cation−olefin closure to form the C-ring in this particular system. Evidently, the bicyclic B-ring cation **8** is a discrete intermediate, and attack by the terminating π-system occurs preferentially at the α-face of C(8) of the bicyclic oxaallylic cation. That mode of closure also controls the C/D-ring fusion of **7** to be *cis*.



We believe that there is a logical mechanistic basis for the realization of the biomimetic A/B-*trans*, 9,10-*syn* cyclization

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(4) The 1:1 mixture of *E*- and *Z*-isomers of **4** could not be separated chromatographically. Further research is planned toward the objective of the stereoselective conversion of **3** to the *E*-isomer of **4**.

(5) The methyl vinyl ether analog of **4** was not a satisfactory substrate for cyclization because the basicity of the methoxy group interfered by coordinating to the Lewis acidic reagent.

(6) The *E*-geometry of the C(7) exocyclic double bond of **5** was also revealed by ^1H NMR NOE data.

(7) The coordinates of **7** and other X-ray data can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

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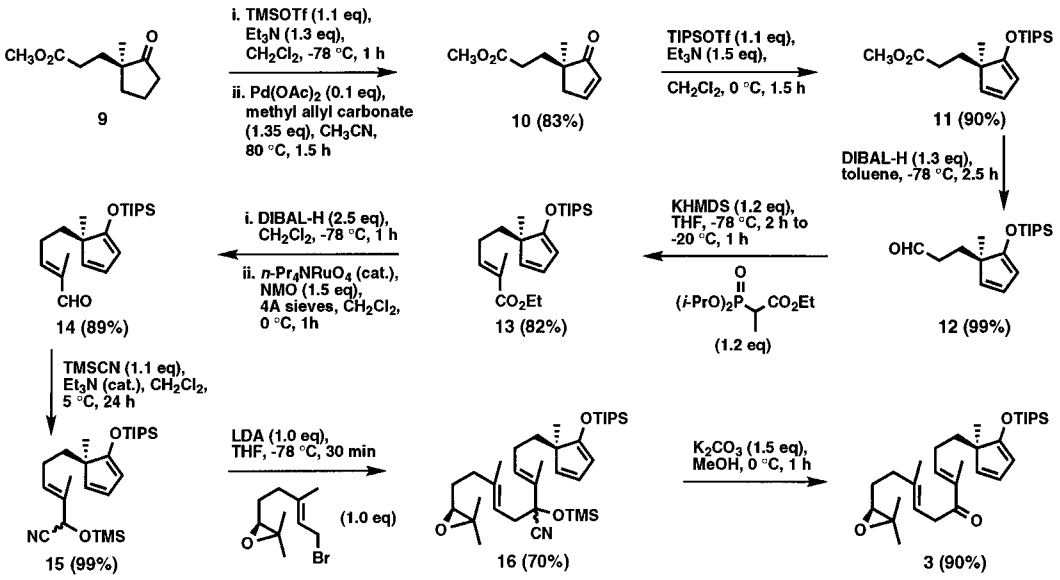
Scheme 1



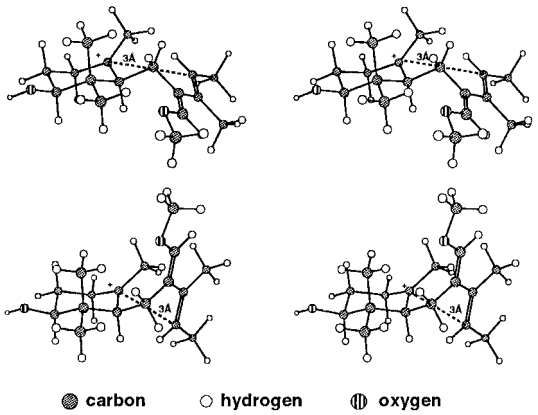


Figure 2. Stereopair representations of alternative transition states in the cyclization of **4**. Top: 9,10-*syn*. Bottom: 9,10-*anti*.

pattern in the chemical conversion of **4** to **5**. Figure 2 presents stereopair representations of possible transition states for the sterol folding (9,10-*syn*) (top) and triterpene folding (9,10-*anti*) (bottom) pathways for the closure of ring B. In both transition states there is planar (i.e., most stable) geometry of the conjugated diene and a 3 Å separation of the carbons which bond during B-ring cyclization.[8] The transition state for 9,10-*syn*-cyclization (top) is clearly more favorable energetically than the transition state for 9,10-*anti*-ring closure (bottom), since the latter involves relatively severe steric repulsion, especially between the methyl group on the cationic center and the methyl substituent on the conjugated diene reaction partner. Thus, the strategic introduction of an additional olefinic linkage into a substrate for cation−olefin cyclization can cause an alteration of transition state geometries and a dramatic shift in the preferred stereochemical course of cyclization. Experiments are in progress to demonstrate the effectiveness of this new strategy in the solution of hitherto formidable synthetic problems, such as the use of the epoxide-initiated cyclization of a polyene to achieve direct formation of the protosterol system.

The synthesis of the intermediate **3** which was required for this study was accomplished by the route outlined in Scheme 1. δ-Keto ester **9**, prepared by enantioselective Michael addition according to Pfau *et al.* (90% ee, 70% yield),[9] was converted via the corresponding α,β-enone (**10**)[10] to the cyclopentadiene ester **11**. Selective reduction of the ester function of **11** gave the aldehyde **12** which upon Horner−Emmons−Wittig chain extension produced the *E*-α,β-unsaturated ester **13**. Dibal reduction of the ester **13** followed by Griffith−Ley oxidation with *N*-methylmorpholine *N*-oxide and catalytic tetra-*N*-propylammonium perruthenate[11] gave the aldehyde **14** which was converted to the TMS ether of the corresponding cyanohydrin **15**. Alkylation of **15** with (*S*)-6,7-oxidogeranyl bromide[12] provided the coupling product **16**[13] which by base-catalyzed deprotection afforded ketone **3**.

Conclusion. A trifluoroethoxymethylene group placed in conjugation with an existing double bond, as in substrate **4**, dramatically alters the face selectivity of cation-initiated cyclization at that double bond. This phenomenon, the basis of which is clarified by the analysis of nonbonded steric repulsion in a transition state model, allows synthetic access to polycyclic products which are not readily accessible by other means. Cation−olefin polyannulation, already an unusually powerful synthetic construction, thereby acquires additional versatility.

Acknowledgment. We are grateful to the National Institutes of Health and the National Science Foundation for generous financial support. The X-ray crystallographic analysis of **7** was carried out by Dr. Marcus Semones.

Supporting Information Available: Experimental procedures, spectroscopic data for compounds **3**−**7** and **9**−**16** and X-ray data for **7** (19 pp). See any current masthead page for ordering and Internet access information.

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(8) The reaction barrier in cation−olefin addition is mainly due to solvent reorganization (cation desolvation−resolvation) and steric effects. In the gas phase there is essentially no barrier to the addition of the *tert*-butyl cation to isobutylene which is 6.5 kcal/mol exothermic at a C−C separation of 3 Å (Prof. William L. Jorgensen, Yale University, personal communication, March, 1996). For such highly exothermic (*ca*. 20 kcal/mol), low activation enthalpy cyclizations, an early transition state is likely and a bonding C−C distance of 3 ± 0.3 Å seems reasonable.

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