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The C-Ring Problem of Sterol Biosynthesis: $TiCl_4$-Induced Rearrangement into the Anti-Markovnikov Cation Corresponding to the C-Ring

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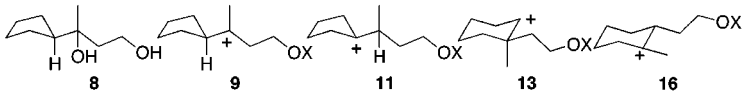
ABSTRACT



Cation 9, generated by the reaction of diol 8 and BF_3·Et_2O, $SnCl_4$, $Sc(OTf)_3$, $FeCl_3$, TiF_4, or CF_3SO_3H, leads to a hydride shift, providing cation 11, which corresponds to the initiation of backbone rearrangement. On the other hand, $TiCl_4$ selectively induces rearrangement to secondary cation 13 by ring expansion, which corresponds to the C-ring formation of sterol biosynthesis. $AlCl_3$ and $ZrCl_4$ induce further rearrangement into six-membered ring *tert*-cation 16.

On the basis of the idea of the stepwise mechanism of biomimetic olefin cyclization[1,2] and enzymatic cyclization of oxidosqualene via conformationally flexible cationic intermediates,[3,4] significant attention has been focused on each step of sterol biosynthesis. Today, the biosyntheses of phytosterols such as dammaranoid, lupanoid, oleananoid, and tirucallanoid are explained by the cyclization of oxidosqualene via bicyclic cation **1**, tricyclic 6/6/5-cation (pre-C ring cation) **2**, secondary 6/6/6-cation **3**, and 6/6/6/5 cation **4** (Scheme 1). In the animal kingdom, steroids are also constructed through the corresponding boat-form B-ring intermediates.[5,6] Recently, we have shown that $^6/_5$ *trans* selective cyclization from **1** to **2** does not depend on any special enzyme effect by achieving a similar Lewis acid-promoted *trans* selective cyclization of **5** to **6**.[7] This may be due to the steric repulsion between the angular methyl and C-12 and C-13 methylenes for $^6/_5$ *cis* cyclization as illustrated

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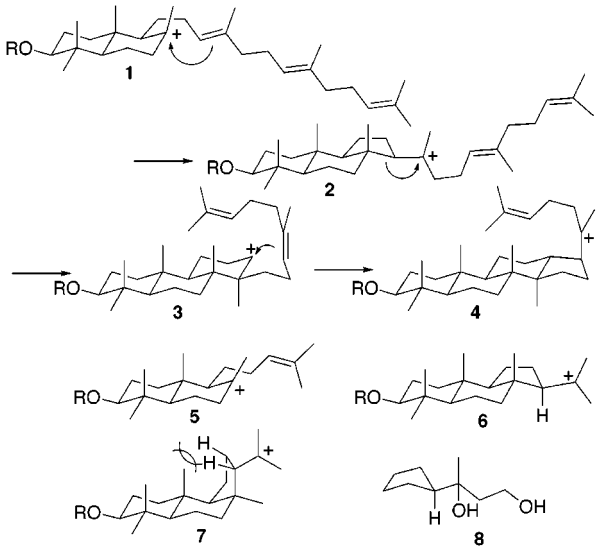
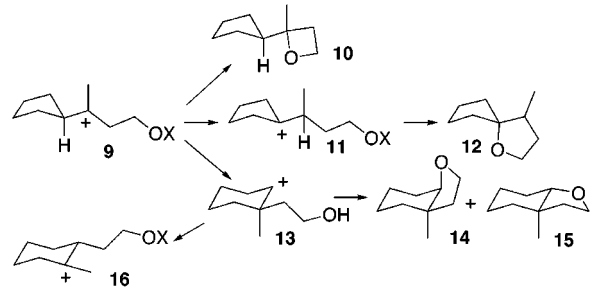
Scheme 1



in **7**.[3c,8] The next problem to be solved was the Markovnikov wall.[3d,9]

Transformation of **2** to **3** involves ring expansion of a tertiary cationic substrate into a secondary cation, namely, an anti-Markovnikov cation. Although related biomimetic[10a,b] as well as chemical[10c,d] rearrangements have been reported, the possibility of achieving the transformation of **2** to **3** as a chemical reaction remained uncertain. We chose diol **8** as the model compound and investigated the chemical behavior of the generated cation **9**. Three possibilities were suggested for the further direction of cation **9** (Scheme 2): (1) direct

Scheme 2



cyclization to give oxetane ring **10**, (2) hydride shift to **11** and cyclization affording spirocyclic tetrahydrofuran **12**, and (3) biomimetic ring enlargement to generate anti-Markovnikov cation **13** leading to **14** or **15**. Although most of the Lewis acids afforded only spiro cyclization product **12** via hydride shift generating cation **11**, $TiCl_4$ surprisingly generated anti-Markovnikov cation **13** selectively. Furthermore, we found that $AlCl_3$ and $ZrCl_4$ selectively led the rearrangement to the unexpected six-membered ring *tert*-cation **16** via **13**.

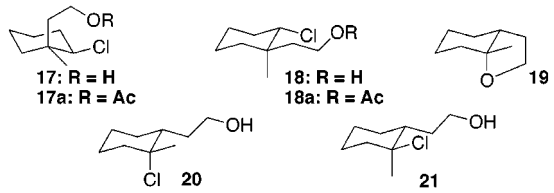
Although diol **8** was inert against $BF_3{\cdot}Et_2O$ (3 equiv) in CH_2Cl_2 under 0 °C, rapid reaction took place at room temperature, affording spirocyclic **12** as the sole product in 82% yield. Reaction of **8** with 3 equiv of $SnCl_4$, $Sc(OTf)_3$, $FeCl_3$, TiF_4, or CF_3SO_3H in CH_2Cl_2 at room temperature for 30 min also provided only the spiro ether **12** as shown in Table 1.

Table 1. Reaction of Diol **8** with Acid and Lewis Acids in CH_2Cl_2

		product (% yield)							
entry	acid	**12**	**14**	**15**	**17**	**18**	**19**	**20**	**21**
1	$BF_3{\cdot}Et_2O$	82							
2	$SnCl_4$	90							
3	$Sc(OTf)_3$	51							
4	$FeCl_3$	76							
5	$FeCl_2$								
6	CF_3SO_3H	88							
7	TiF_4	76							
8	$TiCl_4$	1	16		13	26	9	16	7
9	$TiCl_2(O\text{-}i\text{-}Pr)_2$								
10	$ZnCl_2$								
11	$Zn(OTf)_2$								
12	$AlCl_3$						87		
13	$ZrCl_4$						84		

However, the reaction of **8** with 3 equiv of $TiCl_4$ in CH_2Cl_2 at room temperature afforded an entirely different result. Intensive purification of the complicated reaction mixture provided $^6/_5$ *cis*-fused ether **14** (16% yield), *cis* chloro alcohol **17** (13% yield) and *trans* isomer **18** (26% yield), another $^6/_5$ *cis*-fused ether (**19**, 9% yield), another *cis* chloro alcohol (**20**, 16% yield), and another *trans* chloro alcohol (**21**,7% yield) along with 1% of **12** (Scheme 3). Products **19**−**21**

Scheme 3



should be generated via cation **16** through 1,2-migration of the side chain from **13**. The expected $^6/_5$ *trans*-fused ether **15** was not detected in any reaction.

Reaction of **8** with $AlCl_3$ or $ZrCl_4$ under the same conditions provided another unexpected result. Only double-

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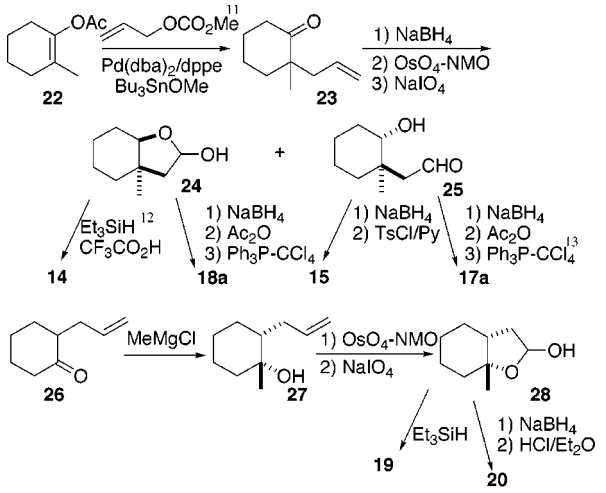
rearrangement and etherification product **19** was obtained in 87% and 84% yields, respectively. Treatment of **8** with $FeCl_2$, $TiCl_2(O\text{-}i\text{-}Pr)_2$, $ZnCl_2$, or $Zn(OTf)_2$ did not provide any reaction product, and most of the starting material was recovered.

Structural studies were carried out carefully by preparing authentic materials as illustrated in Scheme 4.[11−13] Stereo-

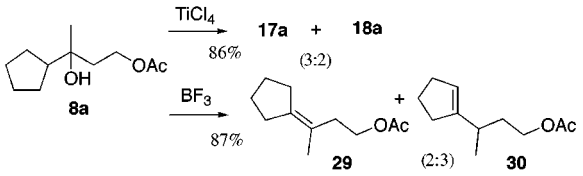
Scheme 4



chemical assignments of **17** and **18** were also achieved by NOE experiments. Clear NOE cross-peaks between the axial methyl group and the axial protons in a 1,3 relationship were detected for **18**, whereas **17** did not show any distinctive NOE cross-peaks between the methyl group and the axial protons. Stereochemical assignments of **20** and **21** were also achieved by NOE experiments.

Since only a small amount of five-membered ring product **12** was detected by the reaction of **8** with $TiCl_4$ (entry 8), we concluded that migration of **9** to anti-Markovnikov cation **13** was controlled with very high selectivity by reflecting the nature of the counteranion. It is also important to note that rather than the expected etherification the predominant reaction path against $TiCl_4$ is chlorination. This should be due to the tight coordination of $TiCl_4$ into a primary alcohol, decreasing the nucleophilicity. Accordingly, next we examined the reaction of acetate **8a**. Upon treatment of **8a** with $TiCl_4$ (2 equiv) in CH_2Cl_2 at room temperature for 1 h, a very clean reaction took place to give a 3:2 mixture of **17a** and **18a** in 86% yield. In sharp contrast, treatment of **8a** with $BF_3{\cdot}Et_2O$ under similar conditions afforded a 2:3 mixture

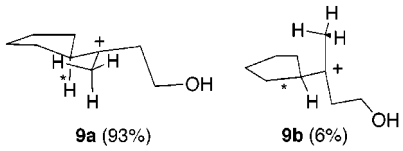
Scheme 5



of **29** and **30** in 87% yield (Scheme 5). Now we can state that the C-ring formation of steroid biosynthesis may be altered without an enzyme. The hydride shift observed in the reactions with most of the Lewis acids is also very important since it corresponds to the initiation of the backbone rearrangement.

It is extremely exciting to consider how the clear selectivity comes about.[14] MM2 calculation of cations **9** using the CAChe-CONFLEX program elucidated the existence of two conformers **9a** and **9b** in 93% and 6% yields, respectively (Scheme 6).[15] The cationic plane of major conformer **9a** is

Scheme 6



perpendicular to the marked C−H bond and favorable for the hydride shift to generate cation **11**. On the other hand, the marked C−C bond of minor conformer **9b** is perpendicular to the cationic plane and favorable for C−C bond migration, affording anti-Markovnikov cation **13**. Detection of the actual conformational change reflecting the nature of the counteranion is the next target of our research.

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Supporting Information Available: Experimental procedures and characterization for compounds **10**, **12**, **14**, **15**, **17**, **18**, **19**, **20**, **21**, **22**, **23**, **24**, **25**, **27**, and **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) When oxetane **10** and spiro ether **12** were treated with $TiCl_4$ in CH_2Cl_2 at room temperature, an ca. 6:3:1 mixture of **14**, **17**, and **18** was formed in nearly quantitative yield. Double rearrangement products such as **19**−**21**were not detected at all.

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