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## The C-Ring Problem of Sterol Biosynthesis: TiCl<sub>4</sub>-Induced Rearrangement into the Anti-Markovnikov Cation Corresponding to the C-Ring

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Cation 9, generated by the reaction of diol 8 and  $BF_3 \cdot Et_2O$ ,  $SnCl_4$ ,  $Sc(OTf)_3$ ,  $FeCl_3$ ,  $TiF_4$ , 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<sub>3</sub> and ZrCl<sub>4</sub> induce further rearrangement into six-membered ring *tert*-cation 16.

On the basis of the idea of the stepwise mechanism of biomimetic olefin cyclization<sup>1,2</sup> and enzymatic cyclization of oxidosqualene via conformationally flexible cationic intermediates,<sup>3,4</sup> significant attention has been focused on

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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.<sup>5,6</sup> 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**.<sup>7</sup> 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.<sup>3d,9</sup>

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<sup>10a,b</sup> as well as chemical<sup>10c,d</sup> 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



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-Markovni-

kov 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<sub>3</sub>, TiF<sub>4</sub>, or CF<sub>3</sub>SO<sub>3</sub>H in CH<sub>2</sub>Cl<sub>2</sub> 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<sub>2</sub>Cl<sub>2</sub>

2 2									
		product (% yield)							
entry	acid	12	14	15	17	18	19	20	21
1	BF <sub>3</sub> •Et <sub>2</sub> O	82							
2	SnCl <sub>4</sub>	90							
3	Sc(OTf) <sub>3</sub>	51							
4	FeCl <sub>3</sub>	76							
5	FeCl <sub>2</sub>								
6	CF <sub>3</sub> SO <sub>3</sub> H	88							
7	TiF <sub>4</sub>	76							
8	TiCl <sub>4</sub>	1	16		13	26	9	16	7
9	TiCl <sub>2</sub> (O-i-Pr) <sub>2</sub>								
10	ZnCl <sub>2</sub>								
11	Zn(OTf) <sub>2</sub>								
12	AlCl <sub>3</sub>						87		
13	ZrCl <sub>4</sub>						84		

However, the reaction of **8** with 3 equiv of TiCl<sub>4</sub> in CH<sub>2</sub>-Cl<sub>2</sub> at room temperature afforded an entirely different result. Intensive purification of the complicated reaction mixture provided  $\frac{6}{5}$  *cis*-fused ether **14** (16% yield), *cis* chloro alcohol **17** (13% yield) and *trans* isomer **18** (26% yield), another  $\frac{6}{5}$ *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** 



should be generated via cation **16** through 1,2-migration of the side chain from **13**. The expected  $\frac{6}{5}$  *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<sub>2</sub>, TiCl<sub>2</sub>(O-*i*-Pr)<sub>2</sub>, ZnCl<sub>2</sub>, or Zn(OTf)<sub>2</sub> 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.<sup>11–13</sup> Stereo-



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<sub>4</sub> (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<sub>4</sub> is chlorination. This should be due to the tight coordination of TiCl<sub>4</sub> into a primary alcohol, decreasing the nucleophilicity. Accordingly, next we examined the reaction of acetate **8a**. Upon treatment of **8a** with TiCl<sub>4</sub> (2 equiv) in CH<sub>2</sub>Cl<sub>2</sub> 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<sub>3</sub>•Et<sub>2</sub>O under similar conditions afforded a 2:3 mixture



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.<sup>14</sup> 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).<sup>15</sup> The cationic plane of major conformer **9a** is



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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<sup>(14)</sup> When oxetane 10 and spiro ether 12 were treated with TiCl<sub>4</sub> 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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