ORGANIC LETTERS

2006
Vol. 8, No. 25
5793−5796

$TiCl_4$ Induced Anti-Markovnikov Rearrangement

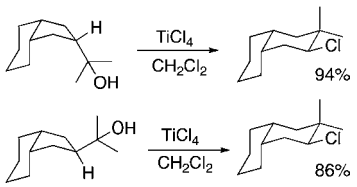
Mugio Nishizawa,* Yumiko Asai, and Hiroshi Imagawa

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770-8514, Japan

mugi@ph.bunri-u.ac.jp

Received September 22, 2006

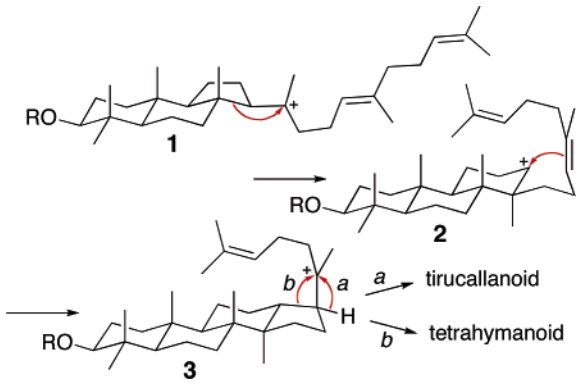
ABSTRACT



Stereoisomeric bicyclic *tert*-alcohols afforded identical ring-expansion products via cationic anti-Markovnikov rearrangement from perpendicular *tert*-cations into identical six-membered ring secondary cations by the treatment with $TiCl_4$. These results provide evidence that the reaction takes place by the cationic stepwise mechanism.

In 1995, Corey and co-workers[1,2] confirmed that the biosyntheses of sterols involves the tricyclic 6/6/5-cation (pre-C-ring cation) **1**, the 6/6/6-cation **2**, and the 6/6/6/5-cation **3** (Scheme 1).[3,4] Hydride shift (*a*) and C−C bond migration (*b*) from **3** are competing processes leading to tirucallanoids and tetrahymanoids, respectively. In the animal kingdom, steroids are also constructed through the corresponding boat-form B-ring intermediates.[1,2,4] The transformation of **1** into **2** involves ring expansion of a *tert*-cation into an unstable *sec*-cation, the so-called anti-Markovnikov rearrangement. The energetic disadvantage of this ring expansion was shown by Jorgensen through calculation of a model cation.[5] Hess as well as Gao have proposed a concerted mechanism from

Scheme 1



(1) (a) Corey, E. J.; Virgil, S. C.; Liu, D. R.; Sarshar, S. *J. Am. Chem. Soc.* **1992**, *114*, 1524−1525. (b) Corey, E. J.; Virgil, S. C.; Cheng, H.; Baker, C. H.; Matsuda, S. P. T.; Singh, V.; Sarshar, S. *J. Am. Chem. Soc.* **1995**, *117*, 11819−11820. (c) Corey, E. J.; Cheng, H. *Tetrahedron Lett.* **1996**, *37*, 2709−2712. (d) Corey, E. J.; Matsuda, S. P. T.; Bartel, B. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 2211−2215. (e) T. Sato, T. Abe, T. Hoshino, *Chem. Commun.* **1998**, 2617−2618.

(2) (a) Hoshino, T.; Sato, T. *Chem. Commun.* **2002**, 291−301. (b) Wendt, K. U.; Schulz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2812−2833. (c) Abe, I.; Rohmer, M.; Prestwich, G. D. *Chem. Rev.* **1993**, *93*, 2189−2206.

(3) (a) Woodward, R. B.; Bloch, K. *J. Am. Chem. Soc.* **1953**, *75*, 2023−2024. (b) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890−1904. (c) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068−5077. (d) Cornforth, J. W.; Cornforth, R. H.; Donninger, C.; Popjak, G.; Shimizu, Y.; Ichii, S.; Forchielli, E.; Caspi, E. *J. Am. Chem. Soc.* **1965**, *87*, 3224−3228. (e) Corey, E. J.; Russey, W. E.; Ortiz de Montellano, P. R. *J. Am. Chem. Soc.* **1966**, *88*, 4750−4751. (f) van Tamelen, E. E.; Willett, J. D.; Clayton, R. B.; Load, K. E. J. *Am. Chem. Soc.* **1966**, *88*, 4752−4754. (g) Johnson, W. S. *Acc. Chem. Res.* **1967**, *1*, 1−8.

(4) (a) Zheng, Y. F.; Abe, I.; Prestwich, G. D. *J. Org. Chem.* **1998**, *63*, 4872−4873. (b) Kushiro, T.; Shibuya, M.; Ebizuka, Y. *J. Am. Chem. Soc.* **1999**, *121*, 1208−1216. (c) Abe, I.; Sakano, Y.; Sodeyama, M.: Tanaka, H.; Noguchi, H.; Shibuya, M.: Ebizuka, Y. *J. Am. Chem. Soc.* **2004**, *126*, 6880−6881. (d) Hoshino, T.; Shimizu, K.; Sato, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 6700−6703.

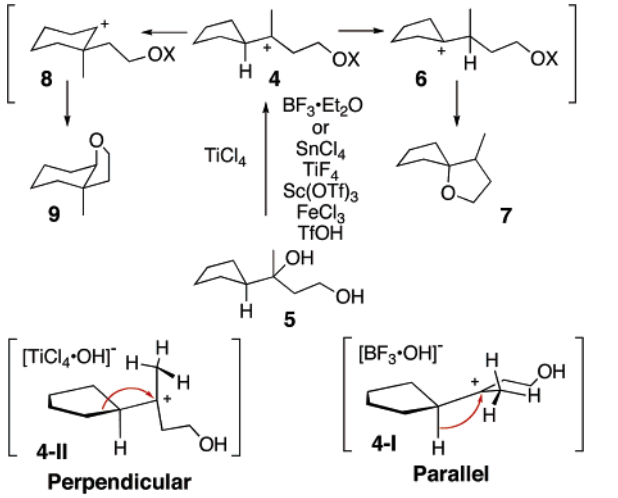
(5) Jenson, C.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1997**, *119*, 10846−10854.

10.1021/ol062337x CCC: $33.50
Published on Web 11/16/2006

1 to **2** on the basis of ab initio calculation of model cations without considering the contribution of counteranions.[6]

We have also reported the C- and D-ring problem from an experimental viewpoint by following the fate of model cation **4**.[7] When the cation was generated by the reaction of diol **5** with a variety of Lewis acids, only the spiro product **7** was obtained via a hydride shift to **6** that corresponds to the conversion *a* from **3**. However, $TiCl_4$ generated the anti-Markovnikov cation **8** selectively and afforded the six-membered ring compound **9** along with other related products, and this result corresponds to the rearrangement

Scheme 2



from **1** to **2** and by following path *b* from **3**. This remarkable selectivity achieved with $TiCl_4$ was explained by the counteranion-controlled conformational changes on the basis of ab initio calculations.[8] We concluded that counteranion $[BF_3{\cdot}OH]^-$ reinforces the parallel conformation **4-I**, from which the hydride shift is the possible transformation. On the other hand, counteranion $[TiCl_4{\cdot}OH]^-$ reinforces the perpendicular conformation **4-II**, from which the migration of C−C bond is the possible transformation. These were, in fact, the first theoretical calculations of cation conformations in the presence of counteranions[9] and the first example to overcome the considerable energy barrier (the "big Markovnikov wall") in cation chemistry. We have achieved generalization of this novel anti-Markovnikov rearrangement by confirming the existence of cationic intermediates.[10]

Now we have prepared hydroxy acetate (*R*)-**10** as an optically active form with 94% ee as seen in chiral GLC (Figure 1a). Treatment of (*R*)-**10** with 3.0 equiv of $TiCl_4$ in

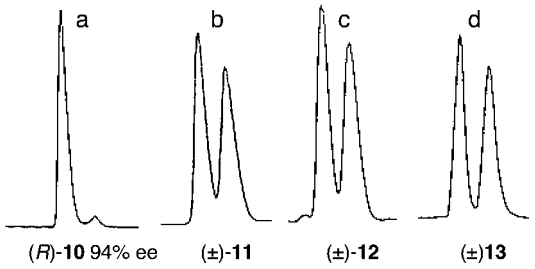
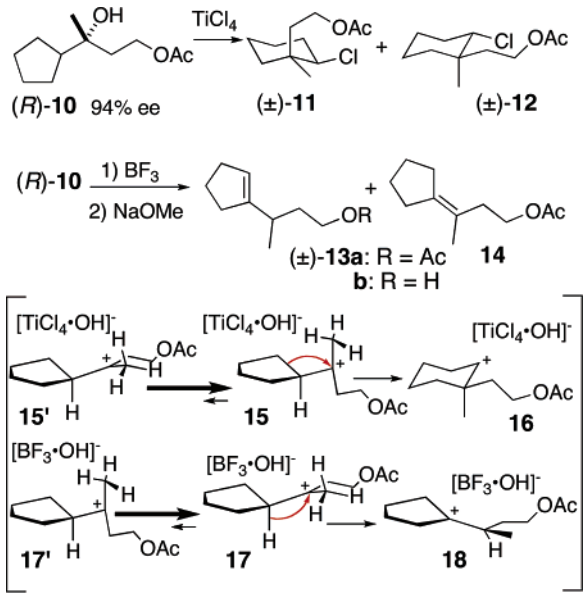


Figure 1. GLC analysis using CHROMPACK Cyclodextrine-b-236M-19 (0.25 × 25 M)

CH_2Cl_2 at room temperature for 2 h afforded a mixture of the anti-Markovnikov rearrangement products **11** and **12** in 93% yield in a 3:7 ratio (Scheme 3). Separation of **11** and

Scheme 3



12 was achieved by HPLC, and the purified **11** and **12** were proved to be racemates as seen in chiral GLC analysis (Figure 1b,c). On the other hand, treatment of the alcohol (*R*)-**10** with 2.1 equiv of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at room temperature for 30 min afforded a 1:1 mixture of alkenes **13a** and **14** in 93% yield. Separation of **13a** and **14** was accomplished by using HPLC. Since baseline separation of **13a** was not achieved on chiral GLC analysis, the acetyl group was cleaved by using NaOMe in MeOH to give alcohol **13b**, and the purified **13b** was shown to be a racemate by chiral GLC (Figure 1d). We conclude that the reaction of (*R*)-**10** with $TiCl_4$ takes place by forming achiral perpendicular cation **15**, followed by rearrangement into racemic six-membered

(6) (a) Hess, B. A., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 10286−10287. (b) Rajamani, R.; Gao, J. *J. Am. Chem. Soc.* **2003**, *125*, 12768−12781. (c) Hess, Jr., B. A. *Org. Lett.* **2003**, *5*, 165−167. (d) Vrcek, V.; Saunders, M.; Kronja, O. *J. Org. Chem.* **2003**, *68*, 1859−1866. (e) Xiong, Q.; Rocco, F.; Wilson, W. K.; Xu, R.; Ceruti, M.; Matsuda, S. P. T. *J. Org. Chem.* **2005**, *70*, 5362−5375.

(7) Nishizawa, M.; Iwamoto, Y.; Takao, H.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2000**, *2*, 1685−1687.

(8) Nishizawa, M.; Yadav, A.; Imagawa, H.; Sugihara, T. *Tetrahedron Lett.* **2003**, *44*. 3867−3870.

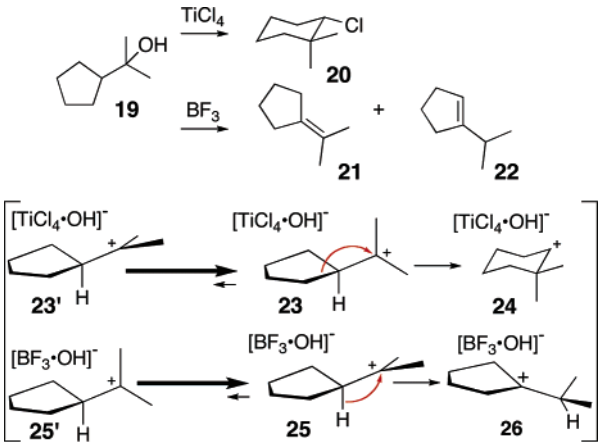
(9) Nishizawa, M.; Yadav, A.; Iwamoto, Y.; Imagawa, H. *Tetrahedron* **2004**, *60*, 9223−9234.

(10) Olah, G. A.; Bollinger, J. M.; Cupas, C. A.; Lukas, J. *J. Am. Chem. Soc.* **1967**, *89*, 2692−2694.

ring secondary cation **16**. The reaction should be terminated by the chloride attack from β-side as well as α-side to form (±)-**11**[7] and (±)-**12**,[7] respectively. Conversely, the reaction with BF_3 generates the achiral parallel cation **17**, and hydride shift takes place to give racemic tertiary cyclopentyl cation **18**. Subsequent deprotonation provides a mixture of alkenes (±)-**13**[7] and **14**.[7] It is not necessary to consider the reaction from parallel cation **15′** and perpendicular cation **17′** due to the significant energy barrier against **15** and **17**, respectively.[8,9]

Next we designed *tert*-alcohol **19**[11] to explore the possibility of the anti-Markovnikov rearrangement of a simple isopropyl cation leading to a six-membered ring secondary cation by using $TiCl_4$. As is the case, the reaction of **19** with 2.0 equiv of $TiCl_4$ at −78 °C for 3 h afforded six-membered ring product **20** in 71% yield (determined by NMR using naphthalene as the internal standard) as the sole product (Scheme 4).[12] On the other hand, treatment with BF_3·Et_2O

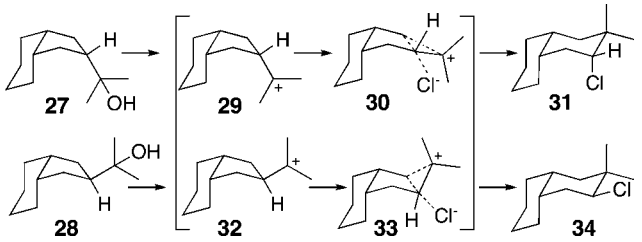
Scheme 4



(1.2 equiv) in $CDCl_3$ at 0 °C for 15 min afforded only hydride shift-deprotonation products **21** and **22** in 61% and 29% NMR yield, respectively.[13] The six-membered ring product **20** should be produced through a rearrangement from perpendicular cation **23** to six-membered ring secondary cation **24**, and the olefinic products **21** and **22** should be formed via the hydride shift from the parallel cation **25** to *tert*-cation **26**. Contribution of parallel conformer **23′** as well as perpendicular conformer **25′** should be negligible due to their large energy barriers against **23** and **25**, respectively.[8,9]

Finally, we designed a reaction of a pair of stereoisomeric *tert*-alcohols **27** and **28** (Scheme 5). If rearrangement takes place by the concerted mechanism from cation to cation as proposed by Hess,[6a] we can expect stereoisomeric rearrangement products, that reflect the stereochemistries of the starting materials. For example rearrangement from **27**

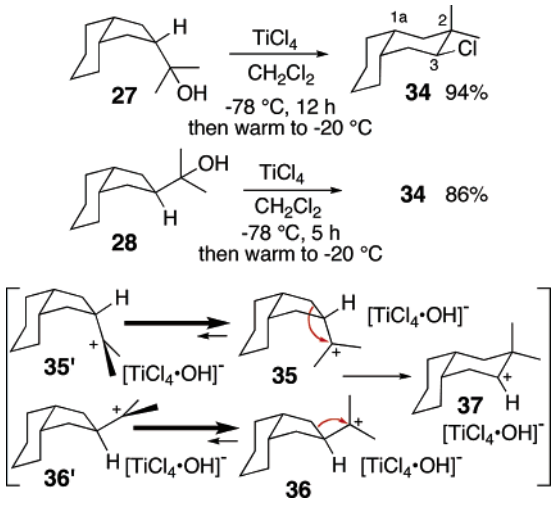
Scheme 5



through *cis*-cation **29** will afford α-chloride **31** via transition state **30**, whereas rearrangement from **28** through *trans*-cation **32** is expected to lead to β-chloride **34** via transition state **33**.

We achieved the reaction of the *cis*-alcohol **27** with 1.2 equiv of $TiCl_4$ at −78 °C for 12 h and the reaction was quenched by the addition of $NaHCO_3$ powder after warming to −20 °C. The reaction cleanly afforded β-chloride **34** in 94% yield as the single product. The 3β equatorial orientation of chloride was confirmed by the detection of a clean double doublet at 3.84 ppm with J = 13.2 and 4.4 Hz. Clear NOE relationships were observed between 1aH-2βMe, 1aH-4βH, 3αH-1αH, 4βH-2βMe, and 1aH-4aH. The reaction of *trans*-alcohol **28** with $TiCl_4$ under the same conditions was also very clean, and the same product **34** was obtained in 86% yield as the sole product (Scheme 6). Thus it is evident that

Scheme 6



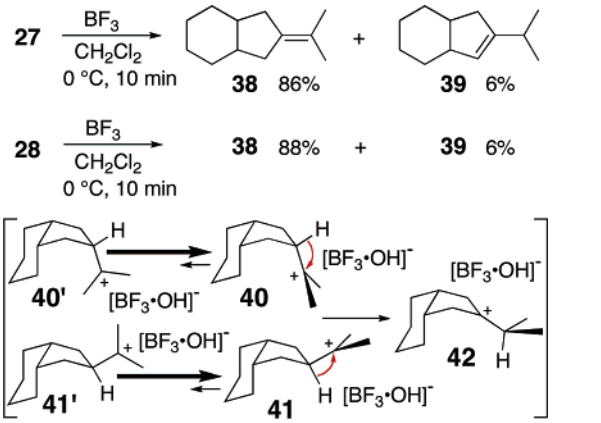
either **27** or **28** generated the same six-membered ring secondary cation **37** from perpendicular cations **35** or **36** via C−C bond migration. The contribution of parallel cation **35′** as well as **36′** are negligible due to the high energy barrier against **35** and **36**, respectively.[8,9] Stereoselective chloride attack to **37** from the convex face resulted in selective formation of **34**. We are therefore able to suggest that the cationic stepwise mechanism for our anti-Markovnikov rearrangement involves controlling the conformation of cationic intermediates by the counteranion $[TiCl_4·OH]^-$.[10]

(11) Mclean, C. D.; Middleton, S. *Aust. J. Chem.* **1978**, *31*, 26599−2667.
(12) Jensen, F. R.; Moder, T. I. *J. Am. Chem. Soc.* **1975**, *98*, 2281−2283.
(13) Apparu, M.; Crandall, J. K. *J. Org. Chem.* **1984**, *49*, 2125−2130.

We are planning to undertake detailed DFT calculation on the conformation of our cationic intermediates, and the result will be described elsewhere.

When **27** and **28** were treated with BF_3·Et_2O (1.2 equiv), tetrasubstituted olefin **38** was obtained as the major product along with a small amount of **39** (Scheme 7). Parallel cations

Scheme 7



40 and **41** should be formed and following hydride shift into the common *tert*-cation **42** should lead to deprotonation to give **38** and **39**. Our earlier Hartree−Fock calculations[8,9] predict that there should be a high energy barrier to the formation of cations **40′** and **41′** from **40** and **41**, respectively. Based on these calculations we presume that it is not necessary to consider them, though further calculations will need to be performed to confirm this unambiguously.

In 1985, we reported the first experimental evidence that olefin cyclization takes place via a stepwise mechanism via conformationally flexible cationic intermediates by trapping each cationic intermediate with water during $Hg(OTf)_2$-induced cyclization of geranylgeranyl acetate.[14] Considered together with the present observations, we propose that the mechanism of sterol biosynthesis occurs via a totally cationic stepwise mechanism. At the active site of the enzyme cavity, the pre-C-ring cation **1** will be reinforced to take a perpendicular conformation controlled by carboxylates of aspartic acid residues along with oxygen functionalities of tyrosine residues, and thereby be rearranged into C-ring secondary cation **2**.[15,16] Therefore, we have elucidated that it is possible to overcome the big Markovnikov wall by cation chemistry.

Acknowledgment. We are grateful to Professor Yasufumi Ohfune of Osaka City University for his kind discussions, and Dr. Masao Toyota of Tokushima Bunri University for GC-MS analysis. This study was financially supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology of the Japanese Government.

Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062337X

(14) (a) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Am. Chem. Soc.* **1985**, *107*, 522−523. (b) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Org. Chem.* **1986**, *51*, 806−813. (c) Nishizawa, M.; Takao, H.; Kanoh, N.; Asoh, K.; Hatakeyama, S.; Yamada, H. *Tetrahedron Lett.* **1994**, *35*, 5693−5696. (d) Nishizawa, M.; Takao, H.; Iwamoto, Y.; Yamada, H.; Imagawa, H. *Synlett* **1998**, 76−78. (e) Imagawa, H.; Iyenaga, T.; Nishizawa, M. *Org. Lett.* **2005**, *7*, 451−453. (f) Imagawa, H.; Iyenaga, T.; Nishizawa, M. *Synlett* **2005**, 703−705.

(15) (a) Lenhart, A.; Weihofen, W. A.; Pleschke, A. E. W.; Schulz, G. E. *Chem. Biol.* **2002**, *9*, 639−646. (b) Lenhart, A.; Reinert, D. J.; Aebi, J. D.; Dehmlow, H.; Morand, O. H.; Schulz, G. E. *J. Med. Chem.* **2003**, *46*, 2083−2092.

(16) The "cationic center" surrounded by the negatively charged amino acid residues such as D376, D374, D377, Y495, Y609, S307, and Y420 of SHC[15] seems to us the real reacting area of every cyclization−rearrangement step. The significance of hydrophobic aromatic amino acid residues such as W169, F601, F605, and F166 is also evident. We envision this area as an "aromatic tunnel" where the polyene chain of flexible conformation slides into the cationic center based on the π, π-interactions.[15] We wish to call this a "Catch and Slide mechanism".