JOC Article

Investigation on the Regioselectivities of Intramolecular Oxidation of Unactivated C−H Bonds by Dioxiranes Generated in Situ

Man-Kin Wong, Nga-Wai Chung, Lan He, Xue-Chao Wang, Zheng Yan, Yeung-Chiu Tang, and Dan Yang*

Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong

yangdan@hku.hk

Received May 23, 2003

We found that dioxiranes generated in situ from ketones **1**−**6** and Oxone underwent intramolecular oxidation of unactivated C−H bonds at δ sites of ketones to yield tetrahydropyrans. From the trans/cis ratio of oxidation products **1a** and **2a** as well as the retention of the configuration at the δ site of ketone **5**, we proposed that the oxidation reaction proceeds through a concerted pathway under a spiro transition state. The intramolecular oxidation of ketone **6** showed the preference for a tertiary δ C−H bond over a secondary one. This intramolecular oxidation method can be extended to the oxidation of the tertiary γ' C−H bond of ketones **9** and **10**. For ketone **11** with two δ C−H bonds and one γ' C−H bond linked respectively by a sp^3 hydrocarbon tether and a sp^2 ester tether, the oxidation took place exclusively at the δ C−H bonds. Finally, by introducing proper tethers, regioselective hydroxylation of steroid ketones **12**−**14** have been achieved at the C-17, C-16, C-3, and C-5 positions.

Introduction

Selective functionalization of saturated hydrocarbons is of significant importance for both basic research and practical applications of organic chemistry. The development of efficient methods for regio- and stereoselective C−H bond activation has attracted considerable attention over the past decades.[1,2] Owing to geometric constraints, intramolecular reactions represent an effective approach for regioselective functionalization of C−H bonds.[3−6] Notably, transition-metal-catalyzed intramolecular C−H bond insertion reactions with carbenes and nitrenes have been extremely useful in organic synthesis.[3] Significant progress has also been made in template-directed remote functionalization and biomimetic regioselective hydroxylation of steroids catalyzed by metalloporphyrin and metallosalen complexes.[4] Furthermore, selective oxidation of remote carbons four bonds away from a hetero-

(1) (a) *Activation and Functionalization of Alkanes*; Hill, C. L., Ed.; Wiley: New York, 1989. (b) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245. (c) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154. (d) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (e) Shilov, A. E.; Shteinman, A. A. *Acc. Chem. Res.* **1999**, *32*, 763. (f) Kakiuchi, F.; Murai, S. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, 1999; pp 47−79. (g) Fokin, A. A.; Schreiner, P. R. *Chem. Rev.* **2002**, *102*, 1551. (h) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (i) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507.

(2) For reviews regarding regioselective oxidation of unactivated C−H bonds, see: (a) Breslow, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 7, Chapter 1.3. (b) Barton, D. H. R.; Doller, D. *Acc. Chem. Res.* **1992**, *25*, 504. (c) Reiser, O. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 69. (d) Breslow, R. *Acc. Chem. Res.* **1995**, *28*, 146. For recent examples on regioselective activation of C−H bonds via organometallic complexes, see: (e) Waltz, K. M.; Hartwig, J. F. *Science* **1997**, *277*, 211. (f) Chen, H.; Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3391. (g) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992. (h) Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995. (i) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633.

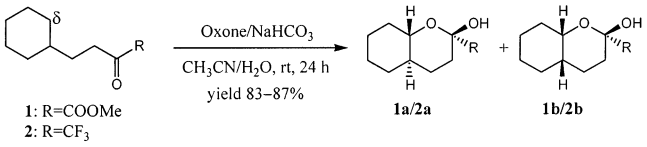
(3) For reviews, see: (a) Moody, C. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 7, Chapter 1.2. (b) Taber, D. F. In *Comprehensive Organic Synthesis*; Pattenden, G., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, Chapter 4.2, p 1045. (c) Doyle, M. P. *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Pergamon Press: New York, 1995; Vol. 12, Chapter 5.2, p 421. (d) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911. (e) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998. For recent examples on carbene and nitrene insertion, see: (f) Taber, D. F.; Stribia, S.-E. *Chem.-Eur. J.* **1998**, *4*, 990 and references therein. (g) Taber, D. F.; Christos, T. E.; Guzei, I. A.; Rheingold, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5589. (h) Barluenga, J.; Rodriguez, F.; Vadecard, J.; Bendix, M.; Fananas, F. J.; Lopez-Ortiz, F.; Rodriguez, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 8776. (i) Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che, C.-M. *Org. Lett.* **2000**, *2*, 2233. (j) Dauban, P.; Dodd, R. H. *Org. Lett.* **2000**, *2*, 2327. (k) Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063. (l) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598. (m) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935. (n) Wehn, P. M.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 12950. (o) Wardrop, D. J.; Zhang, W.; Fritz, J. *Org. Lett.* **2002**, *4*, 489.

(4) (a) Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170. (b) Groves, J. T.; Neumann, R. *J. Org. Chem.* **1988**, *53*, 3891. (c) Groves, J. T.; Neumann, R. *J. Am. Chem. Soc.* **1989**, *111*, 2900. (d) Grieco, P. A.; Stuk, T. L. *J. Am. Chem. Soc.* **1990**, *112*, 7799. (e) Stuk, T. L.; Grieco, P. A.; Marsh, M. M. *J. Org. Chem.* **1991**, *56*, 2957. (f) Kaufman, M. D.; Grieco, P. A.; Bougie, D. W. *J. Am. Chem. Soc.* **1993**, *115*, 11648. (g) Breslow, R.; Zhang, X.; Huang, Y. *J. Am. Chem. Soc.* **1997**, *119*, 4535. (h) Breslow, R.; Huang, Y.; Zhang, X.; Yang, J. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 11156. (i) Breslow, R.; Yang, J.; Yan, J. *Tetrahedron* **2002**, *58*, 653. (j) Breslow, R. *Chemtracts−Org. Chem.* **2002**, *15*, 59.

(5) (a) Barton, D. H. R. *Pure Appl. Chem.* **1968**, *16*, 1. (b) Hesse, R. H. *Adv. Free-Radical Chem.* **1969**, *3*, 83. (c) Walling, C.; Bristol, D. *J. Org. Chem.* **1972**, *37*, 3514. (d) Chow, Y. L.; Danen, W. C.; Nelsen, S. F.; Rosenblatt, D. H. *Chem. Rev.* **1978**, *78*, 243. (e) Turro, N. J. In *Modern Molecular Photochemistry*; Benjamin/Cummings: Menlo Park, CA, 1978; p 386.

10.1021/jo0347011 CCC: $25.00
Published on Web 07/15/2003

SCHEME 1. Selective Oxidation of δ C−H Bond



atom has been successfully accomplished by using the radical reactions that undergo intramolecular 1,5-hydrogen atom abstractions.[5] Nevertheless, there is little progress on the oxidation of more remote unactivated C−H bonds in flexible molecules.[6]

Dioxiranes exhibit excellent reactivities in various oxidation reactions, including epoxidation, heteroatom oxidation, and hydroxylation of unactivated C−H bonds under mild conditions.[7,8] The hydroxylation reaction is completely stereospecific and shows strong preference for tertiary C−H bonds over secondary ones.[8] Both concerted and diradical pathways have been proposed for dioxirane-mediated C−H bond oxidation on the basis of experimental results.[9] Theoretical calculations revealed that dioxirane-mediated hydroxylation of C−H bonds could proceed via a concerted spiro transition state as well as a diradical intermediate.[10]

We previously reported a preliminary study of a novel reaction for oxidation of unactivated C−H bonds at the δ site of ketones (Scheme 1).[11] The observed regioselectivity (i.e., δ selectivity) was different from that of a typical intramolecular radical reaction, suggesting the nonradical nature of this oxidation reaction.[9,10] We thus proposed a concerted C−H bond oxidation mechanism (Figure 1). For ketones **1** and **2**, the δ site oxidation gave a mixture of two fused 1-oxadecalin products with a trans/cis ratio about 4.5:1 (Scheme 1). A spiro transition-state model (Figure 2), in which the two three-membered rings adopt a spiro geometry, was proposed to explain the observed trans selectivity.[11,12] This spiro transition-state model was supported by recent theoretical calculations.[10,13] Here, we report our new investigation on the scope of this hydroxylation reaction. Moreover, we describe the discoveries of (1) a new intramolecular oxidation of tertiary γ′ C−H bonds of ketones and (2) a remote regioselective hydroxylation reaction of steroids.

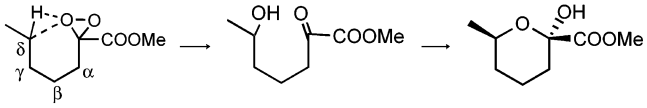


FIGURE 1. Proposed mechanism of intramolecular C−H bond oxidation by dioxirane.

Results and Discussion

1. Synthesis of Ketones 3−13 for Intramolecular Oxidation Reactions. We previously reported that dioxiranes generated from the electronically activated ketones, such as 1,1,1-trifluoromethyl ketones and substituted α-keto esters, showed excellent reactivities in oxidation of unactivated C−H bonds. Therefore, those two electronically activated ketone units were then attached to a series of hydrocarbon chains for oxidation. The general synthetic routes of ketones **3**−**13** are summarized in Scheme 2 (for detailed experimental procedures, see the Supporting Information).

Following Zard's protocol,[14] 1,1,1-trifluoromethyl ketones **3**, **12**, and **13** were readily synthesized by stirring the corresponding carboxylic acid chlorides with trifluoroacetic anhydride and pyridine in CH_2Cl_2. Ketones **4**−**6** were prepared by coupling of the corresponding carboxylic acids and (cyanomethylene)phosphorane in the presence of EDCI followed by oxidative cleavage with

(6) (a) Wagner, P. J.; Kelso, P. A.; Kemppainen, A. E.; Zepp, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 7500. (b) Moreira, R. F.; When, P. M.; Sames, D. *Angew. Chem., Int. Ed.* **2000**, *39*, 1618. (c) Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2000**, *122*, 6321. (d) Dangel, B. D.; Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2001**, *123*, 8149. (e) Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 6900. (f) Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856.

(7) For general reviews on dioxirane chemistry, see: (a) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. (b) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (c) Curci, R. *Advances in Oxygenated Processes*; JAI: Greenwich, CT, 1990; Vol. 2, Chapter 1. (d) Adam, W.; Hadjiarapoglou; Curci, R.; Mello, R. *Organic Peroxides*; Wiley: New York, 1992; Chapter 4. (e) Adam, W.; Hadjiarapoglou, L. P. In *Topics in Current Chemistry*; Springer-Verlag: Berlin, 1993; Vol. 164, p 45. (f) Curci, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811.

(8) For examples on oxidation of unactivated C−H bonds by dioxiranes, see: (a) Murray, R. W.; Jeyaraman, R.; Mohan, L. *J. Am. Chem. Soc.* **1986**, *108*, 2470. (b) Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* **1989**, *111*, 6749. (c) Bovicelli, P.; Lupattelli, P.; Mincione, E.; Prencipe, T.; Curci, R. *J. Org. Chem.* **1992**, *57*, 5052. (d) Bovicelli, P.; Gambacorta, A.; Lupattelli, P.; Mincione, E. *Tetrahedron Lett.* **1992**, *33*, 7411. (e) Adam, W.; Asensio, G.; Curci, R.; Nunez, M. E. G.; Mello, R. *J. Org. Chem.* **1992**, *57*, 953. (f) Asensio, G.; Nunez, M. E. G.; Bernardini, C. B.; Mello, R.; Adam, W. *J. Am. Chem. Soc.* **1993**, *115*, 7250. (g) Bovicelli, P.; Lupattelli, P.; Fiorini, V.; Mincione, E. *Tetrahedron Lett.* **1993**, *34*, 6103. (h) Kuck, D.; Schuster, A.; Fusco, C.; Fiorentino, M.; Curci, R. *J. Am. Chem. Soc.* **1994**, *116*, 2375. (i) Curci, R.; Detomaso, A.; Prencipe, T.; Carpenter, G. B. *J. Am. Chem. Soc.* **1994**, *116*, 8112. (j) Curci, R.; Detomaso, A.; Lattanzio, M. E.; Carpenter, G. B. *J. Am. Chem. Soc.* **1996**, *118*, 11089. (k) Asensio, G.; Castellano, G. Mello, R.; Nunez, M. E. G. *J. Org. Chem.* **1996**, *61*, 5564. (l) Fusco, C.; Fiorentino, M.; Dinoi, A.; Curci, R.; Krause; R. A.; Kuck, D. *J. Org. Chem.* **1996**, *61*, 8681. (m) Adam, W. Curci, R.; D'Accolti, L.; Fusco, C.; Gasparrini, F. Kluge, R.; Paredes, R.; Schulz, M.; Smerz, A. K.; Veloza, L. A.; Weinkotz, S.; Winde, R. *Chem. Eur. J.* **1997**, *3*, 105. (n) Nunez, M. E. G.; Royo, J.; Castellano, G.; Andreu, C.; Boix, C.; Mello, R.; Asensio, G. *Org. Lett.* **2000**, *2*, 831. (o) Curci, R.; D′Accolti, L.; Fusco, C. *Tetrahedron Lett.* **2001**, *42*, 7087. (p) D'Accolti, L.; Fusco, C.; Lucchini, V.; Carpenter, G. B.; Curci, R. *J. Org. Chem.* **2001**, *66*, 9063. (q) Nunez, M. E. G.; Castellano, G.; Andreu, C.; Royo, J.; Baguena, M.; Mello, R.; Asensio, G. *J. Am. Chem. Soc.* **2001**, *123*, 7487. (r) D'Accolti, L.; Kang, P.; Khan, S.; Curci, R.; Foote, C. S. *Tetrahedron Lett.* **2002**, *43*, 4649.

(9) For reports on the mechanism of C−H bond oxidation by dioxiranes, see: (a) Minisci, F.; Zhao, L.; Fontana, F.; Bravo, A. *Tetrahedron Lett.* **1995**, *36*, 1697. (b) Vanni, R.; Garden, S. J.; Banks, J. T.; Ingold, K. U. *Tetrahedron Lett.* **1995**, *36*, 7999. (c) Simakov, P. A.; Choi, S.-Y.; Newcomb, M. *Tetrahedron Lett.* **1998**, *39*, 8187. (d) Bravo, A.; Fontana, F.; Fronza, G.; Minisci, F.; Zhao, L. *J. Org. Chem.* **1998**, *63*, 254. (e) Buxton, P. C.; Marples, B. A.; Toon, R. C. and Waddington, V. L. *Tetrahedron Lett.* **1999**, *40*, 4729.

(10) (a) Shustov, G. V.; Rauk, A. *J. Org. Chem.* **1998**, *63*, 5413. (b) Du, X.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 6480. (c) Glukhovtsev, M. N.; Canepa, C.; Bach, R. D. *J. Am. Chem. Soc.* **1998**, *120*, 10528. (d) Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M.; Rastelli, A. *Tetrahedron Lett.* **2001**, *42*, 2739.

(11) Yang, D.; Wong, M.-K.; Wang, X.-C.; Tang, Y.-C. *J. Am. Chem. Soc.* **1998**, *120*, 6611.

(12) Bach, R. D.; Andres, J. L.; Su, M. D.; McDouall, J. J. W. *J. Am. Chem. Soc.* **1993**, *115*, 5768.

(13) A similar spiro transition state has been found for dioxirane epoxidation reactions. See: (a) Baumstark, A. L.; McCloskey, C. J. *Tetrahedron Lett.* **1987**, *28*, 3311. (b) Baumstark, A. L.; Vasquez, P. C. *J. Org. Chem.* **1988**, *53*, 3437. (c) Baumstark, A. L.; Harden. D. B. *J. Org. Chem.* **1993**, *58*, 7615. (d) Bach, R. D.; Andres, J. L.; Su, M.-D.; McDouall, J. J. W. *J. Am. Chem. Soc.* **1993**, *115*, 5768. (e) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (f) Yang, D.; Wang, X.-C.; Wong, M.-K.; Yip, Y.-C.; Tang, M.-W. *J. Am. Chem. Soc.* **1996**, *118*, 11311. (g) Houk, K. N.; Liu, J.; DeMello, N. C.; Condroski, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10147.

(14) Boivin, J.; Kaim, L. E.; Zard, S. Z. *Tetrahedron Lett.* **1992**, *33*, 1285.

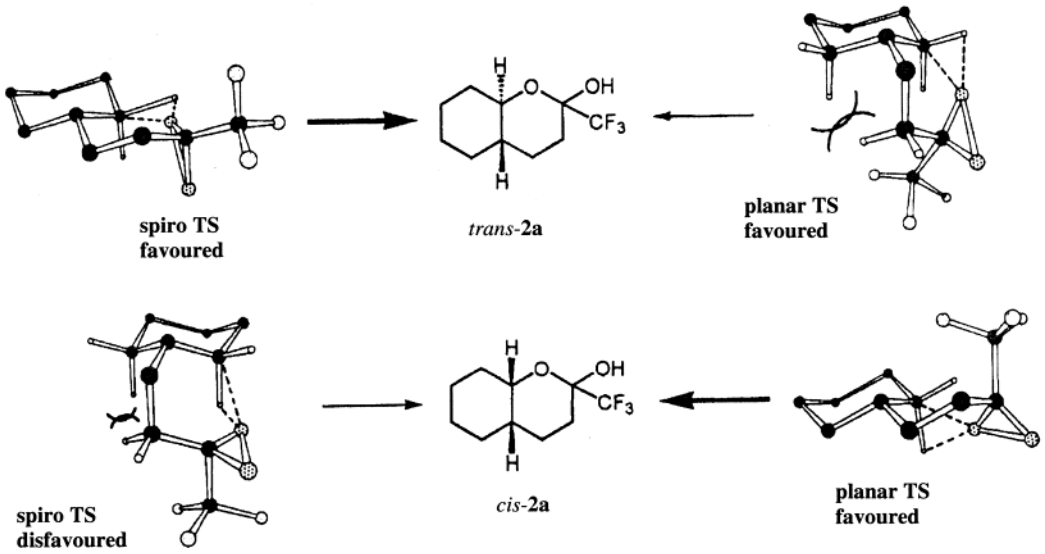
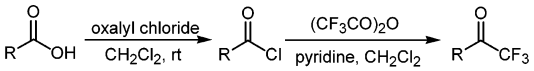


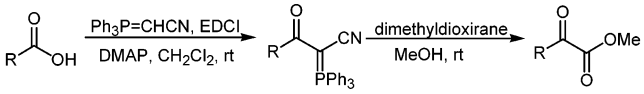
FIGURE 2. Proposed spiro transition state for C−H bond oxidation by dioxirane.

SCHEME 2

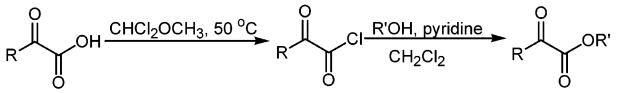
1,1,1-Trifluoromethyl ketones **3**, **12** and **13**:



Ketones **4**–**6**:



Ketones **7**–**11**:



dimethyldioxirane.[15,16] Ketones **7**−**11** were constructed by the coupling reactions of keto acid chlorides with the corresponding alcohols in CH_2Cl_2.

2. δ-Selective Intramolecular Oxidation of Ketones 3−**6.** Ketones **3**−**6** were subjected to the previously reported conditions for intramolecular C−H bond oxidation reactions. The results summarized in Table 1 revealed the δ-selectivity for oxidation of this series of ketones.

Interesting stereoselectivities were observed for the hydroxylation of ketones **3** and **4**. In contrast to the hydroxylation reactions of ketones **1** and **2** bearing a cyclohexane ring, hydroxylation reactions of trifluoromethyl ketone **3** and α-keto ester **4** bearing a cyclopentane ring provided exclusively cis bicyclic products **3a** (74% yield) and **4a** (67% yield), respectively (Table 1, entries 1 and 2). The cis stereochemistry of hemiketal **3a** was confirmed by converting **3a** into known *cis*-lactone **3b** (75% yield) via heating under alkaline conditions (Scheme 3). Hemiketal **4a** could also undergo dehydration to afford *cis*-**4b** in 82% yield upon treatment with MsCl and Et_3N (Scheme 3). The exclusive formation of the cis products **3a** and **4a** may be a result of the closer distance of H_a than H_b to an oxygen atom of dioxirane under a spiro transition state (Figure 3). According to the theoretical calculations on the oxidation of the C−H bond by dioxiranes, the transition state was highly polar and asynchronous, with O−H bond formation much more advanced than that of the C−O bond.[10] Thus, oxidation of the the C−H_a bond could be much faster than that of C−H_b bond.

Oxidation Proceeds with Retention of Configuration. It was known in the literature that oxidation of optically active (*R*)-(−)-2-phenylbutane to (*S*)-(−)-2-phenyl-2-butanol by isolated methyl(trifluoromethyl)-dioxirane and dimethyldioxirane proceeded with complete retention of configuration.[8a,e] This interesting observation prompted us to investigate the stereospecificity of our intramolecular oxidation reactions. Therefore, ketone **5** with a chiral center at the δ-position was prepared from (*S*)-(−)-citronellal (76% ee).[17] Oxidation of ketone **5** afforded the dehydrated cyclic product **5a** in 78% yield together with lactone **5b** in 8% yield (Table 1, entry 3). The optical purity of **5a** was determined to be 73% ee by chiral HPLC analysis, indicating that our intramolecular oxidation reaction proceeded with retention of configuration via a concerted oxygen transfer pathway. The formation of lactone **5b** was probably due to the Baeyer−Villiger rearrangement of the α-keto ester intermediate (Scheme 4).

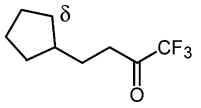
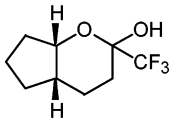
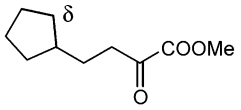
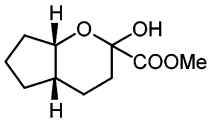
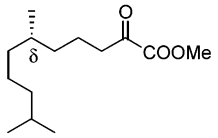
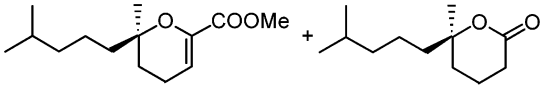
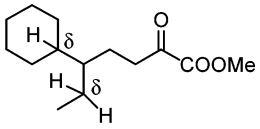
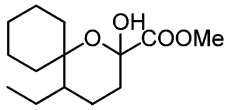
A Strong Preference for Oxidation of Tertiary δ C−H Bonds over Secondary δ C−H Bonds. Ketone **6** has a tertiary δ C−H bond and two secondary δ C−H bonds. Oxidation of **6** took place exclusively at the tertiary δ C−H bond to give **6a** (73% yield), and no product derived from oxidation of secondary δ C−H bond

(15) Wasserman, H. H.; Baldino, C. M.; Coats, S. J. *J. Org. Chem.* **1995**, *60*, 8231.

(16) Wong, M.-K.; Yu, C.-W.; Yuen, W.-H.; Yang, D. *J. Org. Chem.* **2001**, *66*, 3606.

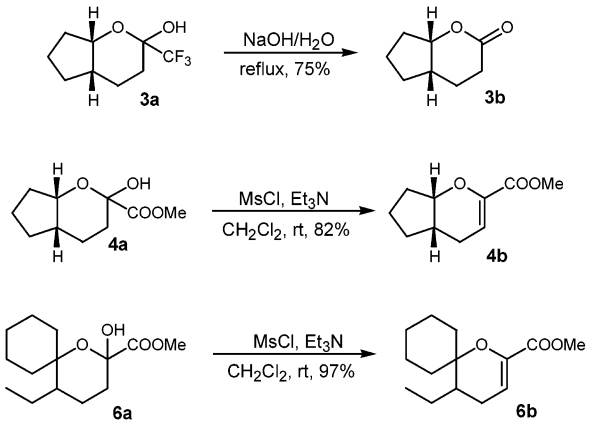
(17) The optical purity of the commercially available (*S*)-(−)-citronellal was determined to be 76% by optical rotation measurement. The optical rotation of commercially available (*S*)-(−)-citronellal was $[\alpha]^{20}_D$ −12.6 (*c* = 1, CH_2Cl_2), and that of optically pure (*S*)-(−)-citronellal is $[\alpha]^{20}_D$ −16.4 (*c* = 1, CH_2Cl_2). See: Becicka, B. T.; Koerwitz, F. L.; Drtina, G. J.; Baenziger, N. C.; Wiemer, D. F. *J. Org. Chem.* **1990**, *55*, 5613.

TABLE 1. Selective Oxidation of δ C−H Bond[a]

entry	ketone	Product (Yield %)[b]
1	 **3**	 **3a** (74%)
2	 **4**	 **4a** (67%)
3[c]	 **5**	 **5a** (78%)[d] **5b** (8%)
4	 **6**	 **6a** (73%)[e]

[a] Unless otherwise indicated, all reactions were carried out with a 10 mM solution of ketone in a 1.5:1 mixture of CH_3CN and aqueous Na_2·EDTA solution (0.4 mM) containing 5.0 equiv of Oxone and 15.0 equiv of $NaHCO_3$ for 24 h at room temperature. [b] Isolated yield after flash column chromatography. [c] Reaction was carried out for 6 h, and the reaction temperature was increased from 0 °C to room temperature after the addition of the mixture of Oxone and $NaHCO_3$. [d] 73% ee; determined by HPLC. [e] **6a** was obtained as a 4:1 mixture of diastereomers.

SCHEME 3



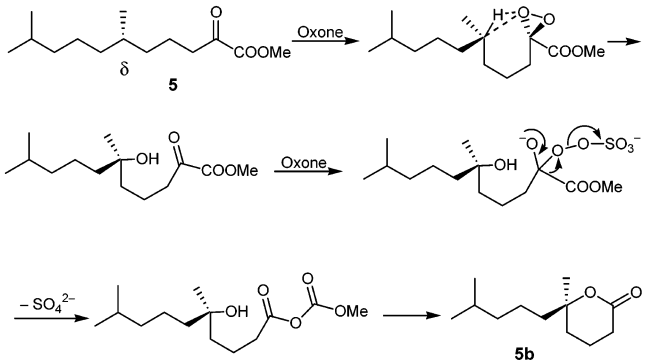
was found (Table 1, entry 4). The complete regioselectivity of this oxidation reaction indicated the strong intrinsic preference for oxidation of tertiary δ C−H bonds over secondary ones, in good agreement with the findings in the literature.[8f] Note that hemiketal **6a** could be converted into **6b** in 97% yield upon treatment with MsCl and Et_3N at room temperature (Scheme 3).

3. A New Intramolecular γ′ C−H Bond Oxidation of Ketones. As mentioned in the above section, we developed a δ-selective C−H bond oxidation method by connecting hydrocarbons and activated ketone groups through tethers consisting of sp^3 carbon atoms. Subsequently, we decided to examine the structural effect of an ester tether on the intramolecular oxidation of **7**−**11** (Table 2).

FIGURE 3. Possible transition state for the oxidation reactions of ketones **3** and **4**.

While ketone **7** has a tertiary δ′ C−H bond and ketone **8** bears two benzylic δ′ C−H bonds, both of them have secondary γ′ C−H bonds adjacent to the oxygen atom of the ester moiety. After ketones **7** and **8** were subjected to our oxidation reaction conditions (10 mM) at room temperature for 72 h, cyclohexanemethanol **7a** and 2-phenylethanol **8a** were obtained in 75% and 93% yields, respectively (Table 2, entries 1 and 2), with no oxidized product detected. Presumably, alcohols **7a** and **8a** came

SCHEME 4. Possible Pathway for the Formation of Lactone 5b



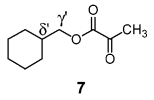
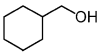
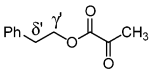
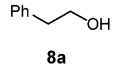
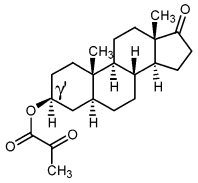
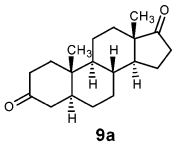
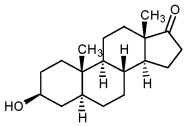
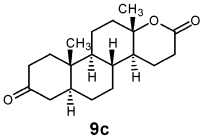
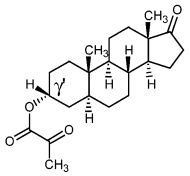
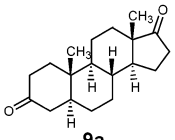
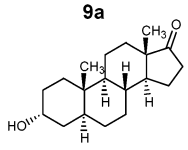
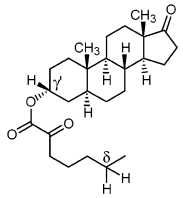
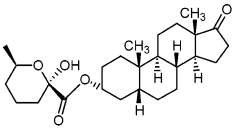
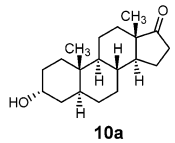
from the ester hydrolysis of ketones **7** and **8** under the high salt conditions. To minimize the rate of ester hydrolysis, we conducted the oxidation at a lower concentration (1.5 mM) with portionwise addition of Oxone. No alcohols could be found under the diluted reaction conditions (1.5 mM) after 120 h, and ketones **7** and **8** remained unchanged (Table 2, entries 1 and 2).

In contrast, oxidation of C3-epimers **9** and **10**, both bearing a tertiary γ' C−H bond, afforded androstane-3,17-dione (**9a**) after 120 h as the major product along with ester hydrolysis products **9b** and **10a** (Table 2, entries 3 and 4). In the oxidation of **9**, a minor product **9c** was also isolated (17% yield), which presumably came from the Baeyer−Villiger oxidation of **9a** by Oxone. Since the hydrolysis of axial ester was slower than that of the equatorial one, the overall oxidation yield for **10** (78%) was higher than that of **9** (61% for the combined yield of **9a** and **9c**). Control experiments indicated that **9a** could not be generated from the intermolecular oxidation of androsterone **9b** and epiandrosterone **10a** by methyl pyruvate and Oxone at the same substrate concentration (1.5 mM). We propose that **9a** is formed through a regioselective intramolecular oxidation of the axial and equatorial tertiary γ' C−H bonds of **9** and **10**, respectively (Figure 4). The dioxirane generated from the ketone moieties of **9** and **10** could bend back to oxidize the γ' C−H bonds under a spiro transition state to afford hemiketals, which were then hydrolyzed to give **9a**. Overall, the oxidation of **9** and **10** to **9a** by Oxone constitutes an alternative to the known photolysis reaction reported by Binkley.[18] The lack of oxidation for **7** and **8** can be explained by the lower activity of their secondary γ' C−H bonds as compared to the tertiary ones in **9** and **10**.

***δ* vs *γ′*-Selectivity in Intramolecular C−H Bond Oxidation Reaction.** The different regioselectivities (i.e., δ or γ' selectivity) observed in the intramolecular oxidation reactions of ketones **1**−**6** and **9**−**10** could be attributed to the structural differences between the sp^3 hydrocarbon tether and the sp^2 ester tether. To investigate the relative reactivity of the intramolecular δ C−H bond and the γ' C−H bond in the oxidation reactions, ketone **11** was designed for such a competition experiment. On one side of the activated ketone group of **11**, there are two secondary δ C−H bonds connected by a tether of three sp^3 carbons. On the other side, there is an equatorial tertiary γ' C−H bond linked by a tether of an ester group (sp^2 hybridized). The oxidation of ketone

TABLE 2. Selective Oxidation of Ketones

ketone —[Oxone/$NaHCO_3$[a], CH_3CN/H_2O, rt]→ product

entry	Ketone	Product	Yield[b] 1.5 mM[c]	Yield[b] 10 mM[d]
1	 **7**	 **7a**	–[e]	75%[f]
2	 **8**	 **8a**	–[e]	93%[f]
3	 **9**	 **9a**	44%[g]	
		 **9b**	38%[g]	
		 **9c**	17%[g]	
4	 **10**	 **9a**	78%[h]	
		 **10a**	20%[h]	
5	 **11**	 **11a**	17%[h]	55%[i]
		 **10a**	77%[h]	45%[i]

[a] 5.0 equiv of Oxone and 15.0 equiv of $NaHCO_3$. [b] Yield based on conversion. [c] The reaction was carried out with a 1.5 mM solution of ketone in a 1.5:1 mixture of CH_3CN and aqueous Na_2·EDTA solution (0.4 mM) for 120 h at room temperature. [d] Reactions were carried out with a 10 mM solution of ketone in a 1.5:1 mixture of CH_3CN and aqueous Na_2·EDTA solution (0.4 mM) for 72 h at room temperature. [e] No reaction. [f] 100% conversion. [g] 88% conversion. [h] 90% conversion. [i] 76% conversion.

(18) (a) Binkley, R. W. *J. Org. Chem.* **1976**, *41*, 3030. (b) Binkley, R. W. *J. Org. Chem.* **1977**, *42*, 1216.

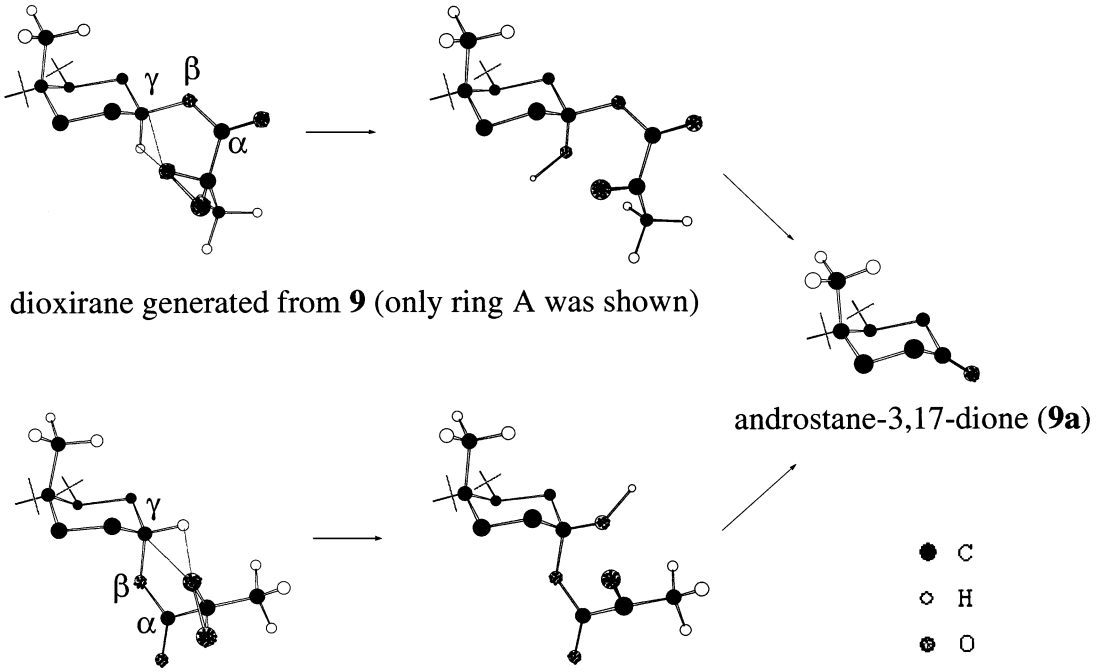


FIGURE 4.

11 was performed at two substrate concentrations, i.e., 10 mM and 1.5 mM (Table 2, entry 5). Under both reaction conditions, hemiketal **11a** and epiandrosterone **10a** were obtained from the oxidation of the δ C−H bond and the ester hydrolysis, respectively. In particular, δ oxidation product **11a** was isolated in 77% yield on the basis of 90% conversion at 1.5 mM concentration. Nevertheless, no product from the oxidation of γ' C−H bond was detected. The outcome of this competition experiment suggested that the oxidation of δ C−H bond at saturated hydrocarbon chains was much more favorable than that of γ' C−H bond. The lower activity of γ' C−H bond of ketones was probably due to the slight distortion of ester bond under a spiro transition state for the intramolecular oxidation reaction (Figure 4).

4. Regioselective Remote Hydroxylation of Steroids. Regioselective remote hydroxylation of steroids is of significant interest in organic synthesis as the oxidized steroids are useful in the synthesis of artificial hormones or steroidal drugs. Recently, hydroxylation of steroids has been achieved by using natural[19] or artificial enzymes,[20] dimethyldioxirane,[21] and other oxidants.[22] Most of those oxidation reactions were carried out in an intermolecular manner. We previously reported one example of the regioselective intramolecular hydroxylation of steroids by using a dioxirane intermediate. Trifluoromethyl ketone **12,** prepared from cholic acid triacetate, gave selective hydroxylation at the 17-position with retention of configuration upon treatment with Oxone (Scheme 5). The observed excellent selectivity promoted us to further explore the remote hydroxylation of steroids. Ketone **13** with one carbon atom less in the tether than **12** was oxidized smoothly at the 16-position (δ-site) to furnish the cis ring junction product **13a** in 77% yield (Scheme 5). These two examples represent a novel pathway for regio- and stereospecific functionalization of steroids.

While dioxiranes generated in situ from **9** and **10** could bend back to oxidize the C-3 hydrogens efficiently and offered androstan-3,17-dione **9a** as the major product (Table 2, entries 3 and 4), oxidation further away from the C-3 hydrogens was not observed, probably because the tether was too short and the dioxirane intermediate could not reach more remote hydrogens. Through building molecular models, we expected that the dioxirane generated from trifluoromethyl ketone **14** might have the

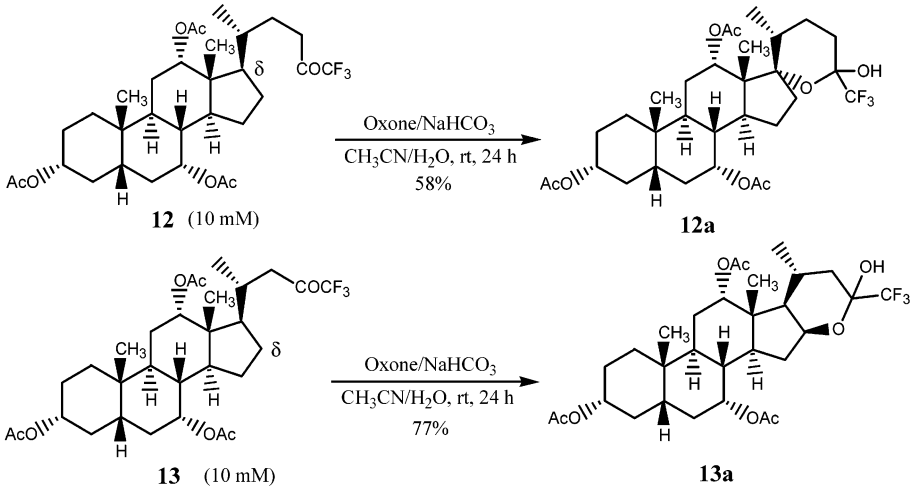
(19) (a) Holland, H. L.; Brown, F. M.; Chenchaiah, P. C.; Chernishenko, M. J.; Khan, S. H.; Rao, J. A. *Can. J. Chem.* **1989**, *67*, 268. (b) Kawaguchi, K.; Hirotani, M.; Furuya, T. *Phytochemistry* **1991**, *30*, 1503. (c) Ortiz de Montellano, P. R., Ed. *Cytochrome P450: Structure, Mechanism and Biochemistry*, 2nd ed.; Plenum: New York, 1995. (d) Woggon, W. D. *Top. Curr. Chem.* **1996**, *184*, 39. (e) Boynton, J.; Hanson, J. R.; Hunter, A. C. *Phytochemistry* **1997**, *45*, 951. (f) Farooq, A.; Hanson, J. R. *Bioscience, Biotechnology, Biochemistry* **1999**, *63*, 1798. (g) Kitamoto, D.; Dieth, S.; Burger, A.; Tritsch, D.; Biellmann, J.-F. *Tetrahedron Lett.* **2001**, *42*, 505.

(20) (a) Yang, J.; Breslow, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2692. (b) Belvedere, S.; Breslow, R. *Bioorg. Chem.* **2001**, *29*, 321. (c) Yang, J.; Gabriele, B.; Belvedere, S.; Huang, Y.; Breslow, R. *J. Org. Chem.* **2002**, *67*, 5057.

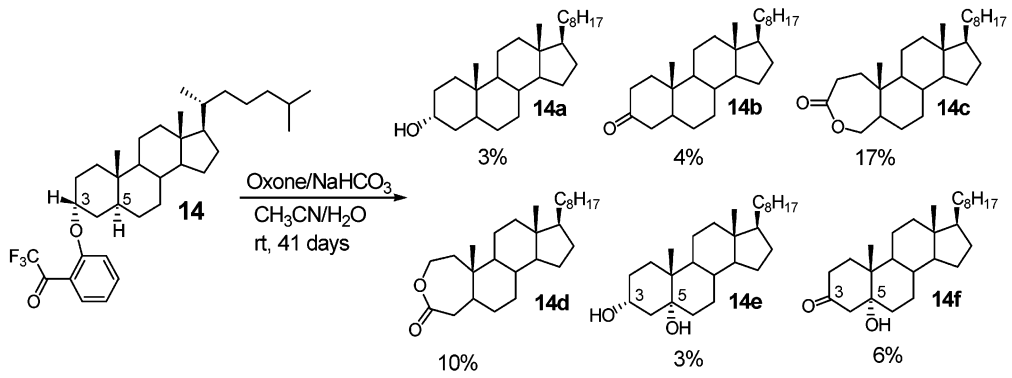
(21) (a) Dixon, J. T.; Holzapfel, C. W.; van Heerden, F. R. *Synth. Commun.* **1993**, *23*, 135. (b) Bovicelli, P.; Gambacorta, A.; Lupattelli, P.; Mincione, E. *Tetrahedron Lett.* **1992**, *33*, 7411. (c) Cerre, C.; Hofmann, A. F.; Schteingart, C. D.; Jia, W.; Maltby, D. *Tetrahedron* **1997**, *53*, 435. (d) Iida, T.; Yamaguchi, T.; Nakamori, R.; Hikosaka, M.; Mano, N.; Goto, J.; Nambara, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2229. (e) Bovicelli, P.; Lupattelli, P.; Fiorini, V.; Mincione, E. *Tetrahedron Lett.* **1993**, *34*, 6103.

(22) (a) Schneider, H. J.; Mueller, W. *J. Org. Chem.* **1985**, *50*, 4609. (b) Tori, M.; Matsuda, R.; Asakawa, Y. *Tetrahedron* **1986**, *42*, 1275. (c) Betancor, C.; Francisco, C. G.; Freire, R.; Suarez, E. *J. Chem. Soc., Chem. Commun.* **1988**, 947. (d) Arnone, A.; Cavicchioli, M.; Montanari, V.; Resnati, G. *J. Org. Chem.* **1994**, *59*, 5511. (e) Betancor, C.; Francisco, C. G.; Freire, R.; Suarez, E. *J. Chem. Soc., Chem. Commun.* **1988**, *14*, 947. (f) Bovicelli, P.; Lupattelli, P.; Fracassi, D. *Tetrahedron Lett.* **1994**, *35*, 935.

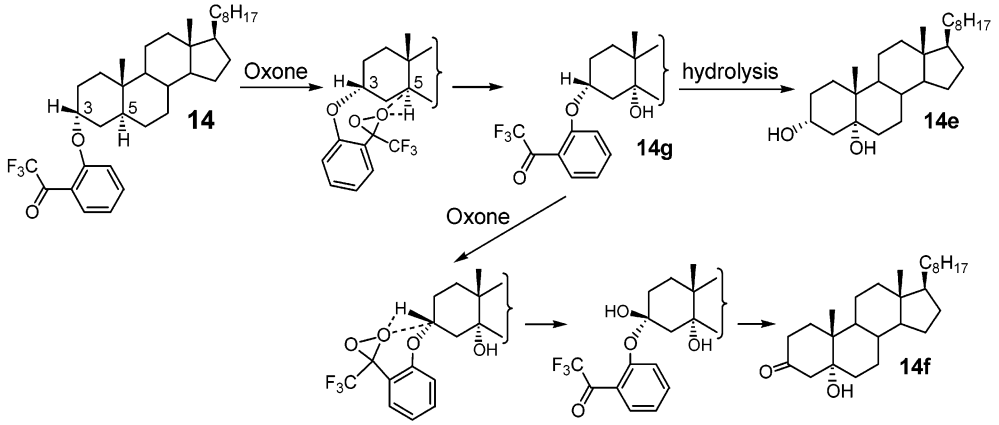
SCHEME 5



SCHEME 6



SCHEME 7



potential to oxidize the remote C-5 hydrogen of cholestanol. Ketone **14**, prepared in two steps from 3β-cholestanol (see the Supporting Information), was stirred in CH_3CN/H_2O (1 mM) with an excess amount of Oxone/$NaHCO_3$ added portionwise at room temperature during a 41-day period. After the reaction, several products were identified (Scheme 6). A trace amount of **14a** (3%) was isolated as the hydrolysis product of ketone **14**. 3-Cholestanone **14b** (4%) was generated from the intramolecular oxidation of the C-3 hydrogen of **14** by the trifluoromethyl dioxirane followed by the hemiketal hydrolysis. The mixture of lactones **14c** (17%) and **14d** (10%) came from the Baeyer−Villiger oxidation of ketone **14b** by Oxone. The isolation of diol **14e** (3%) and keto alcohol **14f** (6%) strongly indicated that regioselective remote hydroxylation occurred at the C-5 position. As outlined in Scheme 7, the dioxirane generated in situ from ketone **14** regioselectively oxidized the C-5 hydrogen to give hydroxyl ketone **14g**, which underwent subsequent hydrolysis to provide diol **14e**. On the other hand, the ketone group of **14g** could generate another dioxirane, which oxidized the C-3 equatorial hydrogen to give keto alcohol **14f**. Though the yield of C-5 oxidation needs further improvement, this is the first example demonstrating the use of a covalently linked dioxirane for regioselective hydroxylation at C-5 positions of steroids.

Conclusions

In summary, we have discovered a highly regioselective method for intramolecular C−H bond oxidation mediated by dioxiranes. The intramolecular oxidation reaction proceeds with retention of configuration and displays a strong preference for tertiary C−H bonds over secondary ones. This δ-selective C−H bond oxidation method allows incorporation of various substituents into the tetrahydropyran products.[23] Furthermore, through modification of the tether linking the ketone group and C−H bonds, we have found a novel dioxirane-mediated intramolecular γ' C−H bond oxidation reaction. Finally, we have successfully demonstrated the feasibility of using covalently linked dioxirane for remote regioselective hydroxylation of steroids.

Experimental Section

General Procedure for Intramolecular δ C−H Bond Oxidation (Table 1, Entry 2). To an acetonitrile solution (43 mL) of ketone **4** (0.13 g, 0.71 mmol) at room temperature was added an aqueous Na_2·EDTA solution (28 mL, 0.4 mM). To this reaction mixture was added a mixture of Oxone (2.17 g, 3.54 mmol) and $NaHCO_3$ (0.88 g, 10.5 mmol). After being stirred at room temperature for 24 h, the reaction mixture was poured into brine and extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (10% EtOAc in *n*-hexane) to give **4a** (0.095 g, 67% yield) as a colorless syrup.

General Procedure for Intramolecular γ' C−H Bond Oxidation (Table 2, Entry 3). To an acetonitrile solution (120 mL) of ketone **9** (0.108 g, 0.3 mmol) at room temperature was added an aqueous Na_2·EDTA solution (80 mL, 0.4 mM). To this reaction mixture was added a mixture of Oxone (0.184 g, 0.3 mmol) and $NaHCO_3$ (0.076 g, 0.9 mmol) at a 24-h interval (total amount of Oxone and $NaHCO_3$ added are 5 × 0.184 g and 5 × 0.076 g, respectively). After the mixture was stirred at room temperature for 120 h, solid NaCl was added until the solution became saturated. The reaction mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (20%−50% EtOAc in *n*-hexane) to give recovered starting material **9** (0.013 g, 88% conversion), **9a** (0.033 g, 78% yield), **9b** (0.029 g, 38% yield), and **9c** (0.014 g, 17% yield) as white solids.

Acknowledgment. This work was supported by the Hong Kong Research Grants Council, The University of Hong Kong, and the Generic Drug Research Program.

Supporting Information Available: Preparation and characterization data of compounds **3**−**11**, **13**, and **14**; NOE assignments of cyclic hemiketals **3a**, **4a**, and **14a**; and HPLC analysis of compound **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0347011

(23) Wong, M.-K.; Chung, N.-W.; He, L.; Yang, D. *J. Am. Chem. Soc.* **2003**, *125*, 158.