Chirality Preservation of a Cation-Radical Intermediate. Tandem Oxidative Ring Expansion–Cyclization Reaction of Optically Active Bicyclo[4.1.0]heptyl Sulfides

Yoshiji Takemoto, Taiichi Ohra, Hiroki Koike, Syun-ichirou Furuse, and Chuzo Iwata*

Faculty of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-Oka, Suita, Osaka 565, Japan

Hirofumi Ohishi†

Osaka University of Pharmaceutical Sciences, 2-10-65 Kawai, Matsubara, Osaka 580, Japan

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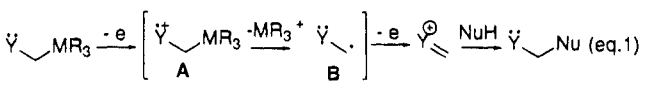
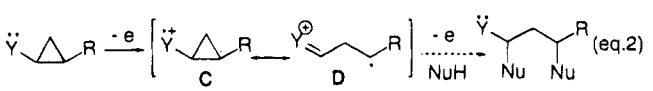
Summary: Asymmetric synthesis of 1-oxaspiro[4.6]-undecan-7-one and spiro[4.6]undecanes has been achieved by a regio- and stereoselective tandem oxidative ring expansion–cyclization reaction of chiral bicyclo[4.1.0]-heptyl sulfides bearing an alcohol or electron-rich olefin in the C-6 side chain *via* a cation radical intermediate.

Recent investigations in the area of electron-transfer chemistry have led to the development of preparatively useful addition and cyclization reactions initiated by photochemical or oxidative electron-transfer from α-metal-substituted heteroatom compounds[1] and electron-rich olefins.[2] In general, the key product-determining step in these processes involves conversion of the initially formed cation-radical species **A** to neutral radical precursors **B** (eq 1). The charge-neutralizing secondary trans-





formations of **A** include loss of group-14-elements (R_3Si and R_3Sn) from sites adjacent to the positively charged centers. The actual routes selected appear to be governed by the nature of the cation-radical species, the types of leaving groups present in the systems, and the solvent. This proposal has been successfully tested in explorations targeted at the development of effective methods for heteroatom (oxygen,[3] nitrogen,[4] and sulfur[5])-substituted radical generation along with loss of the trialkylsilyl and trialkylstannyl group. However, the electron-transfer reactions of heteroatom-substituted cyclopropanes accompanied by C–C bond cleavage are limited to cyclopropanols[6] and their trimethylsilyl ether derivatives[7] except for a few examples of anodic oxidation of 1-alkoxy-2-(phenylthio)cyclopropanes (eq 2).[8] Moreover, there is no report on the stereochemistry of ring-opened products starting from a chiral cyclopropyl substrate in spite of their importance from a mechanistic and biochemical viewpoint.[9] In this paper we wish to report that the ceric ammonium nitrate (CAN) oxidation of chiral cyclopropyl sulfides bearing the hydroxy group or electron-rich olefins leads to regioselective carbon–carbon bond cleavage of cyclopropyl sulfides and stereoselective intramolecular carbon–oxygen or carbon–carbon bond formation (Scheme 1).[10]

We initially examined the SET oxidation of cyclopropyl sulfide **1**[11] bearing no nucleophile in the side chain. Cyclic voltammetry experiments using a glass carbon disk electrode in 0.1 M $NaBF_4/CH_3CN$ (sweep rate 0.1 V/s) revealed that **1** exhibited the first oxidation wave at the peak potential of 1.33 V vs SCE, and therefore we selected CAN as an oxidant.[12] Treatment of **1** with CAN in 10% aqueous methanol (MeOH) at 0 °C instantly led to a regioselective ring-opening of the "a"-bond (depicted in Scheme 1), giving rise to β-methoxy ketone **2**[11] in 72% yield along with a β-hydroxy ketone **3** (23%).[13] Furthermore, to our surprise, **2** was proven to be optically active

† Author to whom correspondence concerning X-ray structures should be addressed.

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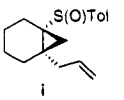
(10) In earlier studies, we have shown that mercury salt serves as a useful reagent for promoting regioselective ring-opening of cyclopropyl sulfides: (a) Takemoto, Y.; Takeuchi, J.; Ohra, T.; Maezaki, N.; Tanaka, T.; Iwata, C. *Chem. Pharm. Bull.* **1993**, *41*, 2034. (b) Imanishi, T.; Ohra, T.; Sugiyama, K.; Ueda, Y.; Takemoto, Y.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1992**, 269. (c) Takemoto, Y.; Ohra, T.; Yonetoku, Y.; Imanishi, T.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1992**, 192.

(11) All starting materials **1**, **4**, **6**, **8**, **10** were prepared from the reported intermediate (**i**) which was determined its absolute configuration by an X-ray crystallographic study.[10b] All new compounds have been characterized by spectroscopic and analytical methods.

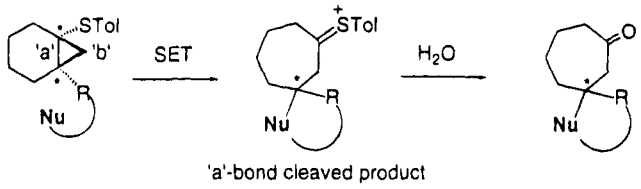


i

(12) Ce^{4+}/Ce^{3+} > 1.5 V vs SCE in water: Dobos, D. *Electrochemical Data*; Elsevier: Amsterdam, 1975; p 245.

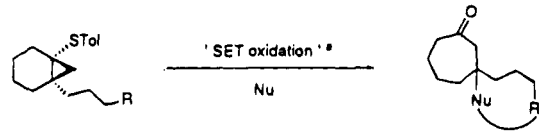
0022-3263/94/1959-4727$04.50/0

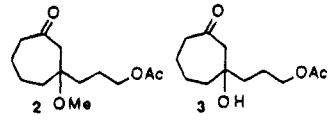
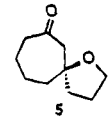
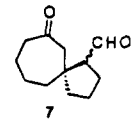
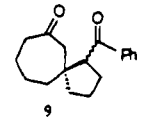
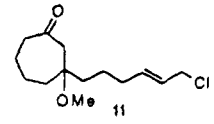
Scheme 1



'a'-bond cleaved product

Table 1. CAN Oxidation of Chiral Cyclopropyl Sulfides



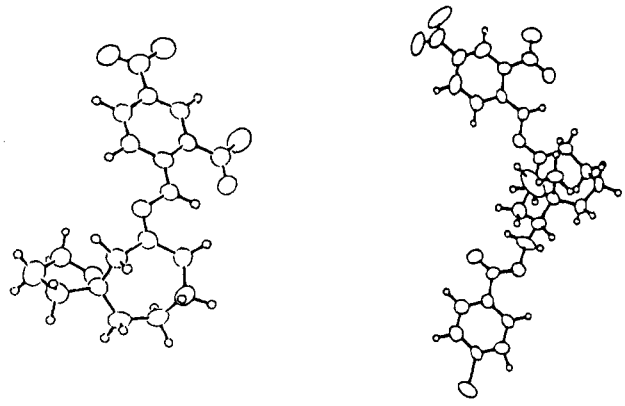
substrate [R]	product	yield (e.e.) (%) [d.e.]
1 [OAc]	 2 OMe 3 OH	2: 72 (67)[b] and 3: 23
4 [OH]	 5	88 (> 90)[c]
6 [CH=CH(OMe)] (*E*/*Z* = 8/5)	 7	73[d] (> 95)[e] [50 : 50][e]
8 [CH=CPh(OTBS)] (*E*/*Z* or *Z*/*E* = 5/2)	 9	52 [74 : 26][e]
10 [CH=CHCH$_2$Cl] (*E* only)	 OMe 11	77

[a] The reactions were normally carried out with 5 equiv of CAN and 5 equiv of K_2CO_3 in 10% aqueous MeOH at 0 °C. [b] The ee was determined from ^{1}H-NMR in the presence of chiral shift reagent [Eu(hfc)$_3$] in $CDCl_3$. [c] These values were determined from HPLC (μ-Porasil with hexane:AcOEt = 25:1 and 8:1) of the MTPA ester **13** and **16**. [d] 10% aqueous CH_3CN was used as solvent. [e] The diastereomeric ratios at C-1 of **7** and **9** were determined from ^{1}H-NMR measurement and isolated yields, respectively.

(but partially racemized; 67% ee) from an NMR experiment in the presence of chiral shift reagent: Eu[(hfc)$_3$].

The present method was also applicable to cyclopropyl sulfides **4**[11] bearing an alcohol in the side chain (Table 1). Regioselective ring-opening and sequential intramolecular nucleophilic cyclization led to exclusive formation of 1-oxaspiro[4.6]undecane **5**[11] in good yield. Furthermore, ^{1}H-NMR experiments of the (+)- and (−)-MTPA esters **13a** and **13b**, derived from **5** by the following sequence, (1) reduction of ketone with L-Selectride at −78 °C (97%), (2) esterification of the resulting diastereomeric pure alcohol with (+)- and (−)-MTPACl (92% and 94%),

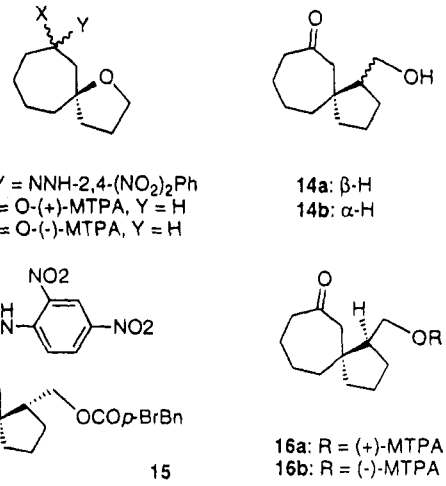
(13) We also found that switching the solvent to dry CH_3CN in place of 10% aqueous MeOH resulted in exclusive formation of the corresponding sulfoxide (76% yield): (a) Fletton, R. A.; Humber, D. C.; Roberts, S. M.; Wright, J. L. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1523. (b) Ho, T. L.; Wong, C. M. *Synthesis* **1972**, 561.



12 15

Figure 1. ORTEP drawings for compounds **12** and **15**.

Scheme 2



revealed that the chirality of **4** was highly preserved (>90% ee) through the intramolecular tandem cyclization reaction (Scheme 2). Next, we investigated the similar tandem oxidative ring expansion−cyclization reaction of the cyclopropyl sulfides **6**, **8**, and **10**[11] bearing olefins in the side chain (Table 1). Whereas the former two compounds furnished the desired spiro[4.6]undecanes (**6** → **7**,[11] **8** → **9**[11]) in moderate yields, the latter failed to cyclize and provided only the undesired ring expanded product **11** in 77% yield. ^{1}H-NMR experiments of the (+)- and (−)-MTPA esters **16a,b**, derived from **7** in two steps [(1) reduction of **7** into **14a,b** with Li(O^{t}Bu)$_3$H in THF at −78 °C (70%); (2) esterification of **14b** with (+)- and (−)-MTPACl in pyridine (85% and 95%)] revealed that the chirality of **6** was also perfectly preserved (>95% ee) through the tandem ring-expansion and spirocyclization process (Scheme 2). Finally, the absolute stereochemistries of these compounds **5** and **7** were determined in order to clarify the reaction mechanism. The 2,4-dinitrophenylhydrazones **12** and **15** were synthesized as yellow crystals from ketones **5** and **14a** in one or two steps [(1) 2,4-dinitrophenylhydrazine (53 and 81% yields), (2) *p*-bromobenzoyl chloride (62% yield)], respectively. The stereochemistry of the quaternary center of **5** and **7** was unambiguously assigned as the *R*-configuration by means of refinement with anomalous scattering factors of **12** and **15** and comparison of the Freidel pair of **12** (Figure 1),[14] which suggests that the intramolecular tandem reaction of **4** and **6** proceeds by inversion in both cases. From the above results, the reaction process could be rationally explained as follows (Figure 2). Initially,

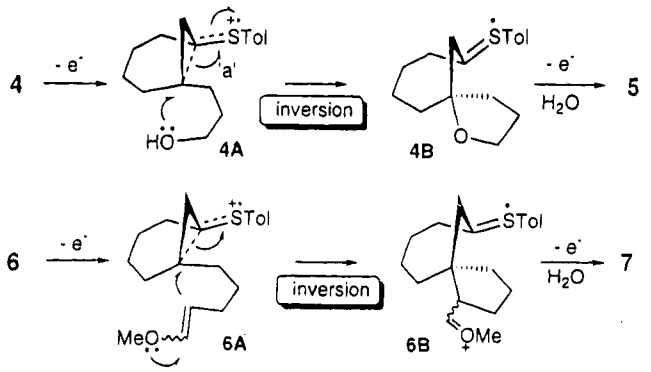


Figure 2. Transition state of oxidative ring expansion of **4** and **6**.

cation radical intermediates like **4A** and **6A** are generated by the SET-oxidation with CAN, and preferential cleavage of the cyclopropyl "a"-bond occurs accompanying with nucleophilic addition of an ω-hydroxy or ω-electron rich olefin group from the back side of C-1 and C-6 bond to give rise to radical intermediates **4B** and **6B**, which are transformed into **5** and **7** by another SET-oxidation and sequential hydrolysis of the resulting sulfonium intermediates.[15]

It is worth noting that nucleophilic heteroatom or electron-rich olefins are necessary to achieve the second intramolecular cyclization. This result differs from the oxidation of cyclopropanol derivatives which succeeded in cyclization with simple C—C double bonds *via* a radical intermediate **D** in the presence or absence of trapping reagents.[6b,7b] In summary, asymmetric synthesis of 1-oxaspiro[4.6]undecane and spiro[4.6]undecanes has been achieved by the intramolecular tandem oxidative ring expansion–cyclization reaction of chiral bicyclo-[4.1.0]heptyl sulfides with chirality preservation of the C-6 carbon center.

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Supplementary Material Available: Procedures for the preparation and full characterization of compounds **1**, **2**, **4**–**9**, **12**, **13a**, **13b**, **15**, **16a**, and **16b** (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) The author has deposited atomic coordinates for **12** and **15** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(15) Anther stepwise mechanism *via* intermediate **D** not **C** (eq 2) can not be excluded at this stage.