The Substituent Effect on Stereoselective Reductive Lithiation of 4,5-Disubstituted 2-Phenylthiooxolane

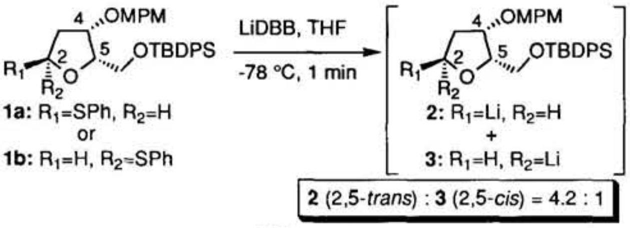
Seiji Amano, Kenshu Fujiwara, and Akio Murai*
Division of Chemistry, Graduate School of Science, Hokkaido University, Sapporo 060-0810

(Received January 12, 1998; CL-980019)

In the reductive lithiation of 2-phenylthiooxolane system, the coexistence of the substituents at C2 and C3 with *cis*-configuration was found to increase the ratio of 2,5-*trans*-2-lithiooxolane to 2,5-*cis* derivative.

Since oxolane is very common structure seen in natural products,[1] 2-lithiooxolanes have been thought to be useful building blocks. However, their applications for actual synthesis are few[2-4] though structurally similar 2-lithiooxane has been used as important segment.[5] One of the reasons for the less applicability is the difficulty of stereoselective generation of carbanionic center in 2-lithiooxolane system. Stereospecific generation *via* tin-lithium transmetalation has been achieved,[3] but the difficulty of the stereo-controlled synthesis of 2-stannyloxolane still remain. The generation of 2-lithiooxolanes by reductive lithiation has also been reported by Cohen,[4] but the stereochemistry in the reaction was unclear. In this context, we have been interested in stereo-controlled synthesis of 2-lithiooxolanes and its application for the synthesis of natural products.

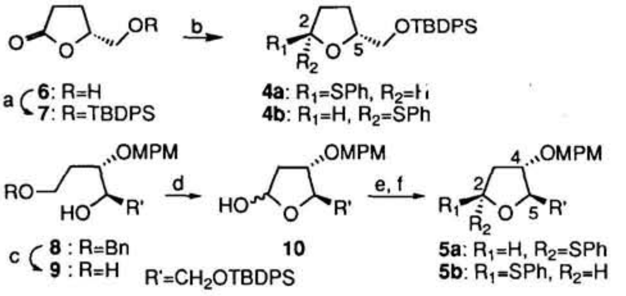
Recently, we have found that 2,5-*trans*-2-lithiooxolane (**2**) could be generated stereoselectively (2,5-*trans* : 2,5-*cis* = 4.2:1) by the reductive lithiation of 4,5-*cis*-disubstituted 2-phenylthiooxolane (**1a** or **1b**) in the course of our synthetic study on pectenotoxins (Scheme 1).[2] To the best of our knowledge, this result seems to be the first example of stereoselective reductive lithiation in the oxolane series.[4] In order to clarify the influence of the MPMO-group at C3 of the 2-phenylthiooxolane to the selectivity of the reaction, we examined the reductive lithiation of 5-substituted (**4**) and 4,5-*trans*-disubstituted 2-phenylthiooxolane (**5**) as well as **1**.



Scheme 1.

The preparation of **4** is shown in Scheme 2. TBDPS ether (**7**), derived from **6**,[6] was subjected to one-pot process (i. DIBAH, ii. $BF_3 \cdot OEt_2$)[4] to give the 2-phenylthiooxolanes (**4a** and **4b**) in 30% and 63% yields, respectively. The synthesis of **5** was started from **8**[2] (Scheme 2). After the selective debenzylation[7] of **8**, the primary hydroxyl group of **9** was oxidized selectively with IBX[8] to produce an inseparable 1:1 mixture of lactols (**10**). Acetylation and the following treatment with PhSH and $BF_3 \cdot OEt_2$[9] of **10** afforded **5a** and **5b** in 23% and 47% yields, respectively.

The result on the reductive lithiation of **1**, **4**, and **5** is shown in Scheme 3. The respective substrates were treated with 3 eq. of lithium 4,4'-di-*tert*-butylbiphenylide (LiDBB)[10] for 10 minutes at -78 °C in THF, and the resulting anions were coupled with 3 eq. of acetone to give alcohols. The diastereomeric ratios of alcohols were responsible to those of the corresponding 2-lithiooxolanes. Each of **4a** and **4b** showed slight *trans*-selectivity (**11a**:**11b**=2:1).[11] On the other hand, **5a** and **5b** afforded the common 1:1 mixture of the adducts (**12**).[11] In the case of **1a** and **1b**, the ratio of 2,5-*trans* : 2,5-*cis* increased to 6:1 regardless of the stereochemistry at C2 of the starting material.[11,12]



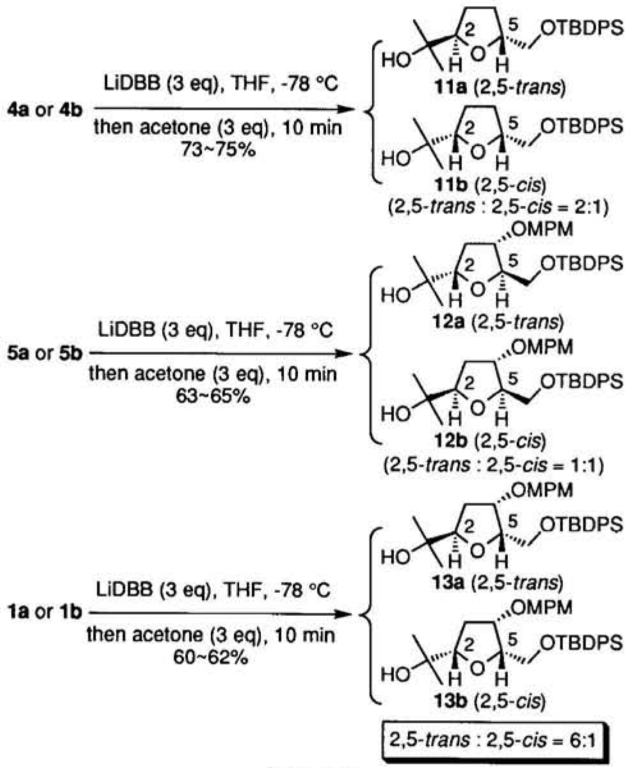
a) TBDPSCl, DMAP, NEt_3, CH_2Cl_2, 20 °C, 2 h (92%); b) DIBAL, CH_2Cl_2, -78 °C, 1 h, then PhSH, $BF_3 \cdot OEt_2$, CH_2Cl_2, -78 °C, 20 min (30% for **4a**, 63% for **4b**); c) Ra-Ni(W2), H_2, EtOH, 20 °C, 24 h (91%); d) IBX, DMSO, THF, 20 °C, 2 h (65%); e) Ac_2O, DMAP, NEt_3, CH_2Cl_2, 0 °C, 30 min (73%); f) PhSH, $BF_3 \cdot OEt_2$, CH_2Cl_2, -78 °C, 2 h (23% for **5a**, 47% for **5b**).

Scheme 2.

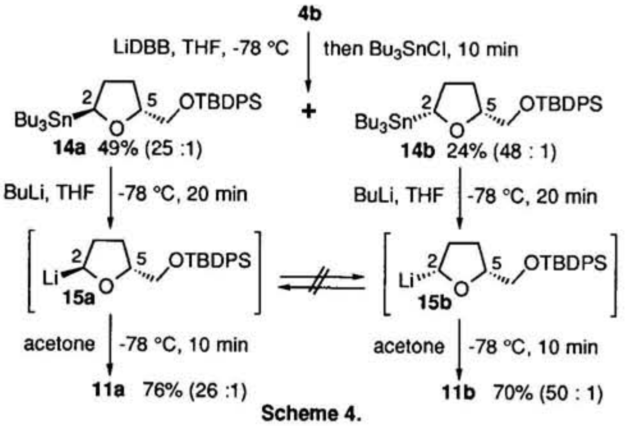
These results reveal some tendency as follows: 1) the substituent at C5 itself preferred 2,5-*trans*-stereoselectivity; 2) the substituent at C4 raised or downed the selectivity depending on its direction; 3) the direction of 2-phenylthio group has no relation with the stereochemistry of the anion. We could realize that coexistence of both the substituents at C4 and C5 with *cis*-configuration is essentially required for high 2,5-*trans*-selectivity in reductive lithiation of 2-phenylthiooxolan system.

Next, we examined whether the equilibrium between two anions could be exist or not under the reaction conditions in our oxolane system (Scheme 4). Still has reported that the transmetalation reaction of an α-alkoxyalkylstannane with BuLi proceeded with retention of configuration.[14] We applied the method for independent generation of two anions (**15a** and **15b**). Starting tributylstannyl compounds (**14a** and **14b**) were prepared by the reaction of anions generated from **4b** with Bu_3SnCl in 49% and 24% yields, respectively. When 2,5-*trans*-compound (25:1 mixture of **14a** and **14b**)[15] was reacted with BuLi at -78 °C for 20 min, the resulting anion gave 2,5-*trans*-adduct (26:1 mixture of **11a** and **11b**)[15] after the reaction with acetone. The same treatment of the requisite 2,5-*cis*-compound (48:1 mixture of **14b** and **14a**)[15] led to *cis*-adduct (50:1 mixture of **11b** and **11a**).[15] It was found that the epimerization did not occur in both the cases during the reaction courses at -78 °C.

We can draw the mode of reductive lithiation in our oxolane system (Scheme 5) based on the hypothesis proposed by Screttas[16]

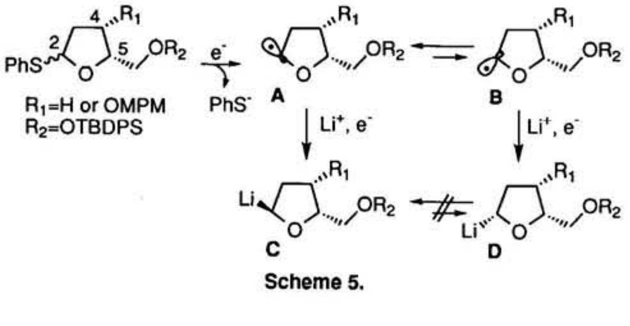


Scheme 3.



Scheme 4.

and Cohen.[4,9] This mechanism is thought to involve two single-electron-transfer (SET) steps: the first is the radical (**A** and **B**) generating step, the second is the anion (**C** and **D**) forming step. Independency of the stereochemistry of the anionic carbon (C2) of 2-lithiooxolanes from that of C2 of the substrates and the absence of the equilibrium between **15a** and **15b** apparently support the existence of the equilibrium between the radical intermediates (**A** and **B**)[17] though our result could not provide the direct proof. Thus, the stereochemistry of the OMPM substituent at C3 might influence the equilibrium between **A** and **B** and/or the reaction rates of second SET steps (**A** → **C** and **B** → **D**).



Scheme 5.

Eventually, the coexistence of both the substituents at C4 and C5 with *cis*-configuration in 2-phenylthiooxolane system is indispensable for stereoselective generation of 2,5-*trans*-2-lithiooxolane by reductive lithiation. This new strategy would provide an efficient mean for the straightforward synthesis of the 2,5-*trans*-dialkylated oxolane system.

One of the authors (S. A.) thanks the Japan Society for the Promotion of Science (JSPS) for a JSPS Research Fellowship for Young Scientists.

References and Notes

1 For example, pectenotoxins; T. Yasumoto, M. Murata, Y. Oshima, M. Sano, G. K. Matsumoto, and J. Clardy, *Tetrahedron*, **41**, 1019 (1985), laureoxolane; A. Fukuzawa, M. Aye, Y. Takaya, H. Fukui, T. Masamune, and A. Murai, *Tetrahedron Lett.*, **30**, 3665 (1989), parvifolorin; S. Ratnayake, Z. Gu, L. R. Miesbauer, D. L. Smith, K. V. Wood, D. R. Evert, and J. L. MacLaughlin, *Can. J. Chem.*, **72**, 287 (1994), and so on.

2 S. Amano, K. Fujiwara, and A. Murai, *Synlett*, **1997**, 1300.

3 Quayle's group has developed a method for diastereoselective synthesis of 3-substituted 2-stannyloxolane and demonstrated its tin-lithium transmetalation. The availability of the method for other oxolane system is unknown. a) Y. Zhao, R. L. Beddoes, and P. Quayle, *Tetrahedron Lett.*, **35**, 4183 (1994). b) Y. Zhao, P. Quayle, and E. A. Kuo, *Tetrahedron Lett.*, **35**, 4179 (1994). c) Y. Zhao, R. L. Beddoes, and P. Quayle, *Tetrahedron Lett.*, **35**, 4187 (1994). d) R. L. Beddoes, M. L. Lewis, P. Quayle, Y. Zhao and M. Attwood, *Tetrahedron Lett.*, **35**, 4189 (1994).

4 T. Cohen and M.-T. Lin, *J. Am. Chem. Soc.*, **106**, 1130 (1984).

5 For example, a) J.-M. Beau and P. Sinaÿ, *Tetrahedron Lett.*, **26**, 6185 (1985). b) R. K. Boeckman, E. J. Enhorm jr., D. M. Demko, and A. B. Charette, *J. Org. Chem.*, **51**, 4754 (1986). c) M. Hoffmann and H. Kessler, *Tetrahedron Lett.*, **35**, 6067 (1994).

6 T. Ishikawa and H. Hidaka, *Meisei Daigaku Kenkyu Kiyo, Rigakubu*, **13**, 31 (1977).

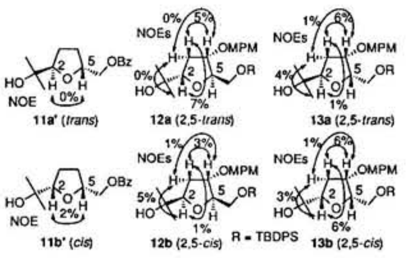
7 Y. Oikawa, T. Tanaka, K. Horita, and O. Yonemitsu, *Tetrahedron Lett.*, **25**, 5397 (1984).

8 E. J. Corey and A. Palani, *Tetrahedron Lett.*, **36**, 3485 (1995).

9 Cf., S. D. Rychnovsky, J. P. Powers, and T. J. LePage, *J. Am. Chem. Soc.*, **114**, 8375 (1992).

10 P. K. Freeman and L. L. Hutchinson, *J. Org. Chem.*, **45**, 1924 (1980).

11 The stereochemistries of **12** and **13** were determined by NOEs. That of **11** could be determined by NOEs of **11'** derived from **11**.



12 It is to be noted that the ratios of the products were slightly different depending upon the electrophiles.

13 Absence of the equilibrium in 3-substituted 2-lithiooxolane system at -78 °C has been reported by Quayle. See ref 3a.

14 a) W. C. Still and C. Sreekumar, *J. Am. Chem. Soc.*, **102**, 1201 (1980). See also, b) J. S. Sawyer, A. Kucerovy, T. L. Macdonald, and G. J. McGarvey, *J. Am. Chem. Soc.*, **110**, 842 (1988). c) K. Tomooka, N. Komine, and T. Nakai, *Tetrahedron Lett.*, **38**, 8939 (1997).

15 In each case, the ratio was determined by HPLC analysis.

16 C. G. Screttas and M. Micha-Screttas, *J. Org. Chem.*, **43**, 1064 (1978).

17 The non-planarity of α-alkoxyalkyl radical carbon has been reported. A. J. Dobbs, B. C. Gilbert, and R. O. C. Norman, *J. Chem. Soc. A* **1971**, 124.