Anionic Ring-Contraction Reaction of Cyclic Acetal System: Stereoselective Approach to Multi-Functionalized Oxetanes

Masaki Suzuki, Katsuhiko Tomooka*

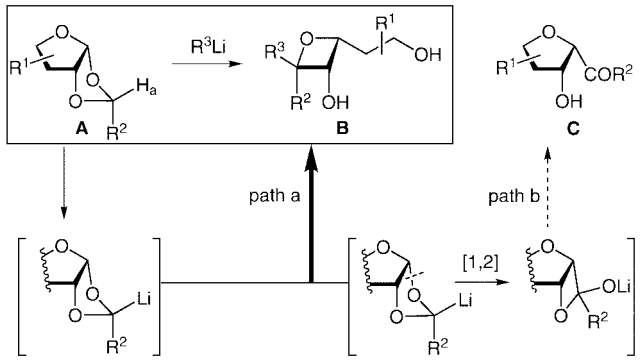
Department of Applied Chemistry, Graduate School of Science and Engineering, Tokyo Institute of Technology, Meguro-ku, Tokyo 152-8552, Japan
Fax +81(3)57343931; E-mail: ktomooka@apc.titech.ac.jp

Received 9 December 2003

Abstract: The reaction of pantolactone derived bicyclic acetal **1** with alkyl lithiums provides 2,2,4-trisubstituted 3-hydroxy oxetane **2** with high diastereoselectivity.

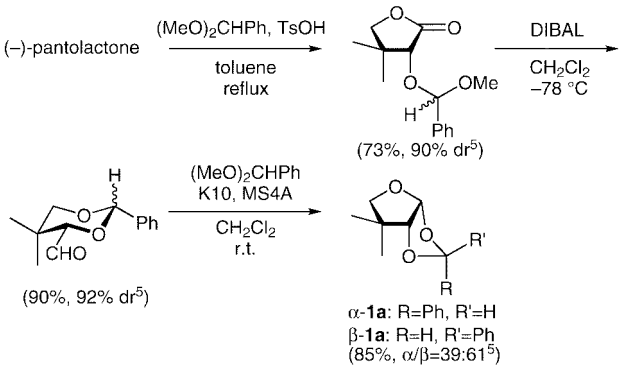
Key words: acetals, carbanions, stereoselective synthesis, oxetanes, rearrangements

Functionalized oxetanes are an attractive synthetic intermediate, which allow unique ring-opening reactions[1] and are present in a variety of biologically active natural products as a key skeleton.[2] Although a number of methods for the synthesis of functionalized oxetanes have been reported, a more efficient approach needs to be developed. Herein, we wish to report a stereoselective approach to the highly functionalized chiral oxetanes **B** by anionic ring-contraction reaction of cyclic acetal **A** (path a in Scheme 1). We have found this novel reaction during the course of study on the [1,2]-Wittig rearrangement.



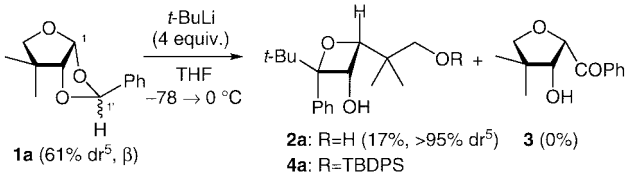
Scheme 1

Recently, we have developed the acetal [1,2]-Wittig rearrangement protocol by which *O*-glycosides (cyclic acetals) can be converted to *C*-glycosides with high diastereoselectivity.[3] Thus, we envisioned that application of the rearrangement protocol to acetal **A** could provide the acyl *C*-glycoside **C** via deprotonation of Ha followed by a ring contractive rearrangement (path b in Scheme 1). To this end, we attempted the reaction of acetal **1a**[4,5] which was successfully prepared as a mixture of C1′ epimers[6] from (–)-pantolactone in three steps: acetal formation with benzaldehyde dimethyl acetal, reduction with DIBAL, and montmorillonite K10 promoted acetal exchange reaction[7] (Scheme 2).



Scheme 2

A reaction of acetal **1a** (α/β = 39:61) was performed by treatment with *t*-BuLi (4 equiv) in THF at –78 °C to 0 °C. To our surprise, the reaction was found to yield unexpected oxetane **2a**[4] in 17% yield as a single diastereomer,[5] but did not give the expected [1,2]-rearrangement product **3** (Scheme 3). The stereochemistry of **2a** was determined by X-ray crystallography of its TBDPS ether **4a** (Figure 1).[8]



Scheme 3

This result means that the unanticipated sequential reactions proceeded which include 1) cleavage of the O-C1′ bond, 2) formation of a carbon-carbon bond between C1 and C1′, 3) introduction of a *t*-Bu group derived from *t*-BuLi to the C1′ position, 4) ring-opening of five-membered acetal. To clarify the generality of this novel reaction, next we examined a similar reaction of **1a** with MeLi, *n*-BuLi and *s*-BuLi. As shown in Scheme 4, all of these reactions provide the corresponding oxetanes **2b**–**d**[4,5,8–11] in moderate to good yield with excellent diastereoselectivity.

SYNLETT 2004, No. 4, pp 0651–0654
Advanced online publication: 10.02.2004
DOI: 10.1055/s-2004-817772; Art ID: U27303ST

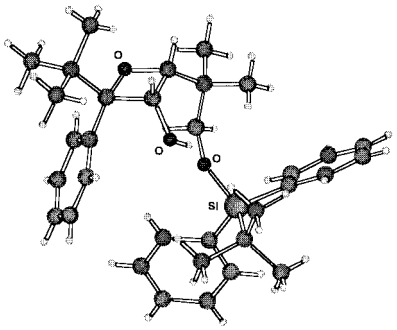
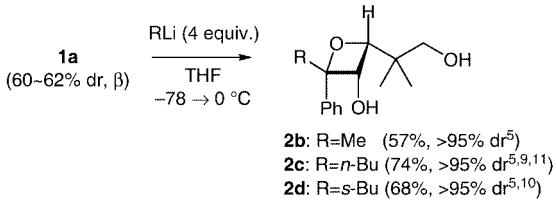
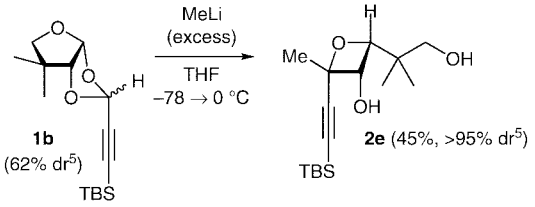


Figure 1



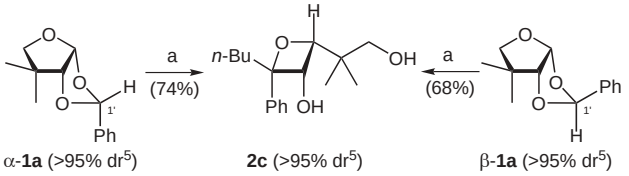
Scheme 4

Furthermore, we have found that a similar reaction can occur in the propargyl acetal system. A reaction of propargylic acetal **1b**[12] (81% dr at C1′) with MeLi in THF gave alkynyl substituted oxetane **2e**[4–6] in 45% yield, also as a single diastereomer (Scheme 5).



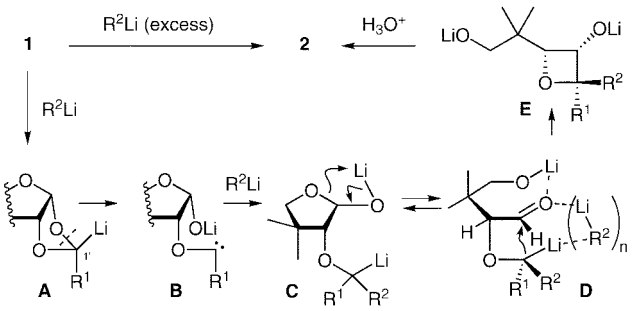
Scheme 5

In order to gain insight into the steric course of the reaction, next we examined the reaction of diastereochemically enriched α-**1a** and β-**1a**. As a result, reaction of α-**1a** and β-**1a** provided the same stereoisomer of oxetane **2c**, and the yields are not significantly different (Scheme 6). These results reveal that the stereochemistry of C1′ of the substrate does not affect the stereochemistry of the product. In other words, the reaction is stereoselective, but is not stereospecific at the acetal C1′ chirality.



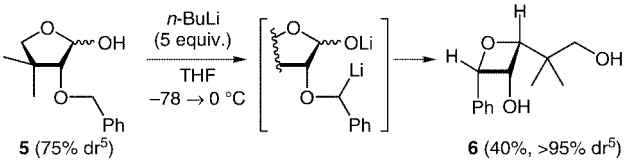
Scheme 6 *Reagents and conditions*: a) *n*-BuLi (4 equiv), THF, –78 °C to 0 °C.

A plausible mechanism of this oxetane formation reaction is shown in Scheme 7. The mechanism most likely involves the carbene intermediate **B** which is formed by the O-C1′ bond cleavage in acetal anion **A**.[13,14] Then, the resulting carbene **B** inserts into alkyl lithium[14] to form the lactol alkoxide **C** which then isomerizes into aldehyde **D**. At the end, aldehyde **D** undergoes an intramolecular nucleophilic addition reaction to form oxetane **E**.[15] The key to this process is the generation of the lactol alkoxide **C**, which acts as a masked aldehyde, and reacts only with an intramolecular nucleophile but does not react with the alkyl lithium reagent.



Scheme 7

To confirm the postulated reaction pathway from lactol alkoxide **C** to oxetane **E**, we examined the reaction of pantolactol derived benzyl ether **5**[5,16] with excess amount of *n*-BuLi (Scheme 8). As expected, the reaction gave oxetane **6**[4,5,17] (>95% dr) as a major product, albeit in moderate chemical yield.



Scheme 8

In summary, we have described a highly diastereoselective approach to multi-functionalized oxetane by the anionic ring-contraction reaction of cyclic acetal. The investigation into the scope and limitation, detailed reaction mechanism as well as its synthetic applications are under way in our laboratory.

Acknowledgment

This research was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas (A) 'Exploitation of Multi-Element Cyclic Molecules', Basic Area (B) No. 14350473 and the 21st Century COE Program 'Creation of Molecular Diversity and Development of Functionalities' from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References

(1) Reviews: (a) Porco, J. A.; Schreiber, S. L. In *Comprehensive Organic Synthesis*, Vol. 5; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, **1991**, 151–192. (b) Abe, M.; Nojima, M. *J. Synth. Org. Chem., Jpn.* **2001**, *59*, 855.

(2) For example: (a) Thromboxane A_2: Bhalgwat, S. S.; Still, W. C. *J. Am. Chem. Soc.* **1985**, *107*, 6372. (b) Oxetin: Kawata, Y.; Ikekawa, N.; Murata, M.; Omura, S. *Chem. Pharm. Bull.* **1986**, *34*, 3102. (c) Oxetanocin: Nishiyama, S.; Yamamura, S. *J. Synth. Org. Chem., Jpn.* **1991**, *49*, 670. (d) Merrilactone A: Birman, V. B.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2080.

(3) (a) Tomooka, K.; Yamamoto, H.; Nakai, T. *J. Am. Chem. Soc.* **1996**, *118*, 3317. (b) Tomooka, K.; Yamamoto, H.; Nakai, T. *Angew. Chem. Int. Ed.* **2000**, *39*, 4500.

(4) All new compounds were fully characterized by IR, ^{1}H and ^{13}C NMR analyses. Data for selected compounds are as follows. Compound α-**1a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55–7.52 (m, 2 H), 7.40–7.38 (m, 3 H), 5.98 (d, *J* = 3.9 Hz, 1 H), 5.85 (s, 1 H), 4.13 (d, *J* = 3.9 Hz, 1 H), 3.84 (d, *J* = 8.1 Hz, 1 H), 3.54 (d, *J* = 8.1 Hz, 1 H), 1.14 (s, 3 H), 1.07 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.0, 129.6, 128.4, 126.7, 106.2, 104.7, 88.0, 77.2, 43.0, 24.0, 17.9. Compound β-**1a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.44 (m, 2 H), 7.40–7.37 (m, 3 H), 6.09 (s, 1 H), 6.03 (d, *J* = 3.6 Hz, 1 H), 4.23 (d, *J* = 3.6 Hz, 1 H), 3.78 (d, *J* = 8.6 Hz, 1 H), 3.69 (d, *J* = 8.6 Hz, 1 H), 1.20 (s, 3 H), 1.07 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.5, 129.5, 128.4, 126.4, 106.0, 105.7, 88.1, 80.1, 43.0, 25.0, 18.9. IR (neat): 2963, 2873, 1460, 1393, 1222, 1074, 1027, 1008 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.16; H, 7.26. $[\alpha]_D^{28}$ +29.4 (*c* 3.67, $CHCl_3$). Compound **2a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 7.8 Hz, 1 H), 7.41–7.36 (m, 1 H), 7.26–7.25 (m, 3 H), 5.10 (br s, 1 H), 4.92 (d, *J* = 7.4 Hz, 1 H), 4.44 (d, *J* = 7.4 Hz, 1 H), 3.63 (d, *J* = 10.4 Hz, 1 H), 3.00 (d, *J* = 10.4 Hz, 1 H), 1.60 (br s, 1 H), 0.96 (s, 12 H), 0.84 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.2, 128.8, 127.6, 127.2, 126.5, 125.9, 95.9, 88.7, 70.0, 66.7, 39.4, 37.4, 24.7, 24.4, 19.8. IR (reflection): 3235, 2925, 1473, 1391, 1364, 1169, 963, 709, 598 cm^{-1}. Compound **2e**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.26 (d, *J* = 7.0 Hz, 1 H), 4.16 (dd, *J* = 11.3, 7.0 Hz, 1 H), 3.55 (d, *J* = 11.1 Hz, 1 H), 3.40 (dd, *J* = 11.1, 5.3 Hz, 1 H), 2.60 (d, *J* = 11.3 Hz, 1 H), 2.09 (br s, 1 H), 1.63 (s, 3 H), 0.99 (s, 3 H), 0.97 (s, 9 H), 0.93 (s, 3 H), 0.19 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 103.0, 95.1, 94.1, 82.8, 72.1, 70.0, 37.3, 26.5, 26.2, 20.0, 19.4, 16.6, –4.39, –4.44. IR (neat): 3418, 2956, 2928, 2857, 1472, 1363, 1251, 1123, 835, 777 cm^{-1}. Compound **6**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.29 (m, 5 H), 5.89 (br s, 1 H), 5.45 (dd, *J* = 2.7, 2.4 Hz, 1 H), 4.56 (br s, 2 H), 4.04 (d, *J* = 10.5 Hz, 1 H), 3.43 (d, *J* = 10.5 Hz, 1 H), 1.74 (br s, 1 H), 1.10 (s, 3 H), 1.01 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.0, 128.6, 128.3, 128.1, 125.5, 125.3, 91.4, 90.8, 74.4, 66.6, 39.6, 23.5, 20.2. IR (neat): 3332, 2958, 2929, 1454, 1134, 1047, 972, 698 cm^{-1}.

(5) The diastereomer ratio was determined by ^{1}H NMR analysis.

(6) The relative stereochemistry of α-**1a** and **2e** was determined by NOE experiment as shown below (Figure 2).

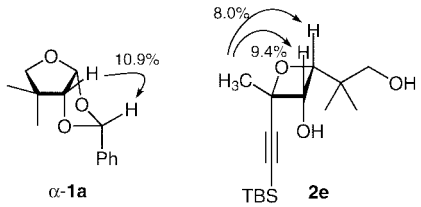
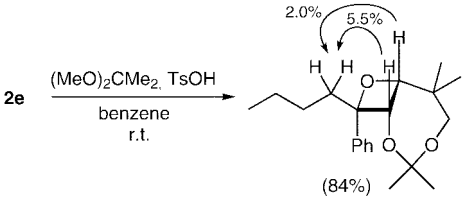


Figure 2

(7) (a) Trost, B. M.; Edstrom, E. D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 520. (b) Tomooka, K.; Nakamura, Y.; Nakai, T. *Synlett* **1995**, 321.

(8) Crystallographic data of **4a** and **2b** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 225890 and 225891, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK [fax: +44 (1223)336033; e-mail: deposit @ccdc.cam.ac.uk].

(9) The relative stereochemistry of **2c** was determined by NOE experiment of its acetal derivative as shown below (Scheme 9).

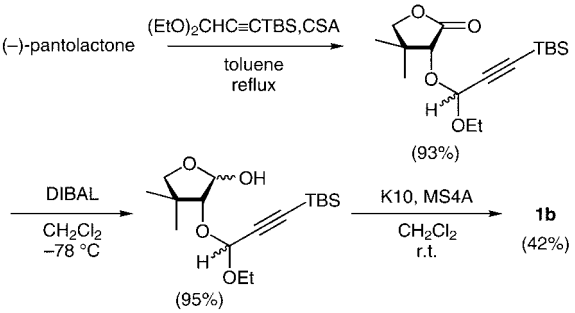


Scheme 9

(10) The substrate **2d** consisted of a 1:1 mixture of two epimers at the chirality center of *s*-Bu.

(11) **General Procedure for the Ring-Contraction Reaction:** To a THF (9 mL) solution of **1a** (72.4 mg, 0.33 mmol, 62% dr) was added *n*-BuLi (1.04 mL, 1.27 M in hexane, 1.32 mmol) dropwise at –78 °C. After the addition, the solution was stirred for 15 min at –78 °C, and the temperature was allowed to rise to 0 °C over a period of 1 h. The resulting mixture was stirred at 0 °C for 1 h, and then sat. NH_4Cl aq was added. The mixture was extracted with Et_2O. The combined organic phase was dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (hexane/Et_2O = 1:1) to give the oxetane **2c** (67.8 mg, 74%, >95% dr). In the case of the reaction with MeLi, >10 equiv of MeLi was required to drive the reaction to completion.

(12) Acetal **1b** was prepared from (–)-pantolactone in three steps as shown below (Scheme 10).



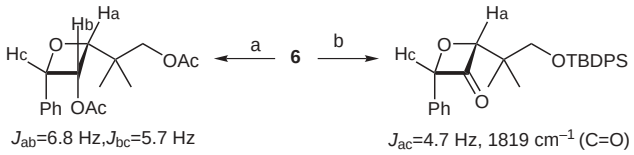
Scheme 10

(13) We cannot rule out the possibility that the reaction proceeds via not a free carbene but a related carbenoid intermediate.

(14) The alkyl lithium-promoted carbene or a related carbenoid formation in acetal system, followed by its insertion to alkyl lithium has been reported, see: (a) Shiner, C. S.; Tsunoda, T.; Goodman, B. A.; Ingham, S.; Lee, S.; Vorndam, P. E. *J. Am. Chem. Soc.* **1989**, *111*, 1381. (b) Boche, G.; Bosold, F.; Lohrenz, J. C. W.; Opel, A.; Zulauf, P. *Chem. Ber.* **1993**, *126*, 1873.

(15) The exact origin of the observed stereoselectivity is not clear at present, while it might be considered as the result of i) stereoselective formation of benzylic or propargylic chiral carbanion by the diastereoselective carbene insertion to alkyl lithium (**B**→**C**) and/or the efficient epimerization (at **C** or **D**), followed by ii) diastereoselective addition reaction via the chelation intermediate (**D**).

(16) The lactol **5** was prepared from pantolactone(racemic) in two steps: benzylation of the hydroxy group with benzyl bromide, half-reduction with DIBAL.



J_{ab}=6.8 Hz,J_{bc}=5.7 Hz

J_{ac}=4.7 Hz, 1819 cm^{-1} (C=O)

Scheme 11 *Reagents and conditions*: a) Ac_2O; b) TBDPSCl; Dess–Martin periodinane.

(17) The structure of **6** was determined by ^1H NMR analysis and IR analysis of its derivatives as shown below (Scheme 11). It is known that the oxetane-3-one displays a carbonyl absorption in the IR spectrum at about 1820 cm^{-1}, see: Thijis, L.; Cillissen, P. J. M.; Zwannenburg, B. *Tetrahedron* **1992**, *48*, 9985.