Rapid Access to in Situ Generated (*R*)- and (*S*)-2-Furyloxirane and Associated Regioselective Nucleophilic Ring-Opening Studies

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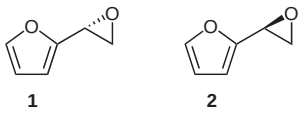
Abstract: Reported herein is the facile preparation of (*R*)- and (*S*)-2-furyloxirane from D- and L-tri-*O*-acetyl glucal and associated regioselective nucleophilic ring-opening studies.

Key words: epoxide, furan, nucleophilic ring opening, regioselectivity, Umpolung effects

Chiral 2-furyloxirane (i.e. **1**, Figure 1) is a versatile building block in organic synthesis that has been pivotal in the total synthesis of some complex natural products.[1] Procedures to access **1** and **2** in high enantiomeric purity are, however, limited and those available require an asymmetric hydrogenation step in the synthetic sequence.[1,2] The volatility, thermal and light instablity of 2-furyloxirane add to the problem in utilizing this valuable building block more widely. Considering the demand in our own work, the limited synthetic protocols available and the undesirable physical properties, we investigated practical solutions to overcome these issues surrounding (*R*)-**1** and (*S*)-2-furyloxirane (**2**).

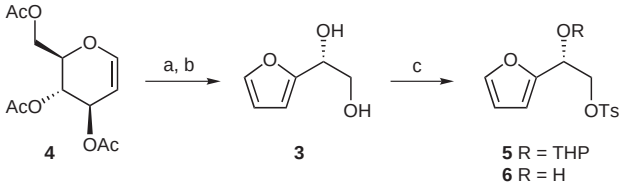


1 **2**

Figure 1

In the view that (*R*)-diol **3** is readily prepared in two easy steps[3] from commercial tri-*O*-acetyl-D-glucal[4] (**4**) in high enantiomeric purity and the THP-protected tosylate **5** has been described,[5] we entertained the notion that if the unprotected primary tosylate **6** could be controlled then the desired epoxide (i.e. **1**) would most likely be achievable on treatment with base (Scheme 1).

Although (*R*)-diol **3** had been reported the protocol described[3d] was not amenable to scale-up, however, after minor modification[6] (*R*)-diol **3** could be obtained in 82% yield on a 20 mmol scale. Selective tosylation of the primary alcohol proceeded without difficulty[5] giving (*R*)-**6** in near-quantative yield.[7,8] The enantiomeric (*S*)-tosylate **7** can be produced from tri-*O*-acetyl-L-glucal, obtained from L-glucose.[10]



Scheme 1 *Reagents and conditions*: a) cat. NaOMe, MeOH, r.t., 4 h, quant.; b) 5 mol% $FeCl_3 \cdot 6H_2O$, MeCN, r.t., 1 h, 82%; c) 1.2 equiv TsCl, pyridine, r.t., 17 h, 95%.

Formation of 2-furyloxirane **1** and **2** was readily achieved by treating a diethyl ether solution of tosylate **6** or **7**, respectively, with 2 molar equivalence of sodium hydride (60% in mineral oil) under an argon atmosphere at room temperature (30 min). For practical reasons **1** (or **2**) was never isolated but subsequently used in situ without difficulty as evidenced below.

Interestingly, ring-opening studies of chiral 2-furyloxirane (i.e. **1**) with carbon or hetero nucleophiles have not been performed. Merely a handfull of reactions with basic organometallic reagents and racemic 2-furyloxirane has been reported.[11] Reactions with amines, alcohols, carboxylic acids, and metal hydrides have been reported but again with racemic 2-furyloxirane.[12] This suggested a more detailed study was required to allow the wider community to understand both reactivity and regioselectivity of nucleophilic ring opening, with a major focus on carbon nucleophiles.

Due to the basic nature of carbon nucleophiles it was envisioned that excess use of the nucleophile would deprotonate tosylate **6**, facilitating formation of epoxide **1**, and then the second equivalent of nucleophile would furnish ring-opened products. This approached either failed or produced low yields of product, for example, *n*-BuLi did not lead to the expected product, most likely due to lithiation of the furan ring. Hence, the protocol of choice was to first generate **1** in situ using sodium hydride followed by addition of the nucleophile.

Lithiated TBS-dithiane was investigated in the first instance, which initially gave a mixture of C1- and C2-opened furyl TBS ethers **8** and **9** (Figure 2) resulting from an intramolecular Brook rearrangement[13] (entry 1, Table 1). Addition of HMPA gave again a mixture of both regioisomers favoring **9** (entry 2, Table 1), but also increased the yield. The diasteromeric ratio could be further

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improved at lower temperatures, but this decreased yields significantly. Switching to TMEDA inverted the regioselectivity toward C1 attack (entry 5, Table 1), with comparable yield. Unsubstituted dithiane, much to our surprise, afforded **10** (60%) as the sole product, which, to the best of our knowledge, is the first reported C2-selective ring opening of a furyloxirane. Alteration of the reaction conditions, including investigation of additives, did not lead to a variation in regioisomers only downward fluctuation in yields.

Table 1 Reaction with Lithiated TBS-dithiane[14]

Entry	Additive	Temp	Ratio of **8**:**9**[a]	Yield (%)[b]
1	None	r.t.	22:78	45
2	HMPA	r.t.	60:40	50
3	HMPA	0 °C	63:37	40
4	HMPA	–78 °C		n.r.[c]
5	TMEDA	r.t.	10:90	65

[a] Determined after separation by column chromatography.
[b] Isolated yield of major isomer.
[c] n.r. = no reaction.

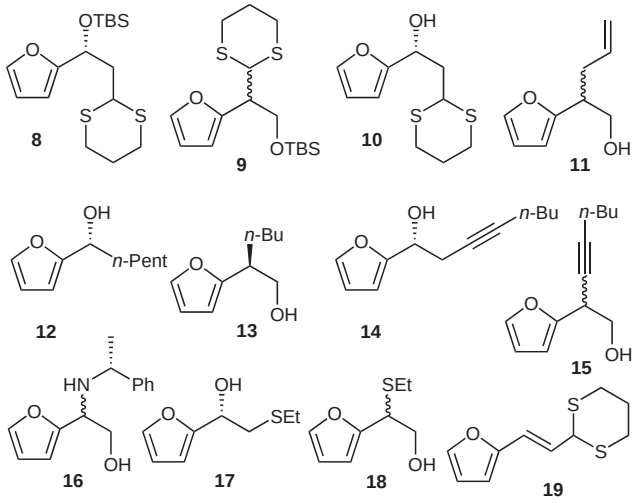

Figure 2

The Grignard reagent allylmagnesium bromide gave in all cases racemic ring opening at C1 (i.e. **11**) as observed by Pae et al.,[11b] with the highest yield obtained using HMPA (80%).

Interestingly, addition of butyl cuprate[15] to tosylate **6** at low temperature resulted in exclusive attack at C2 (**12**) in 68% yield, whereas lithium hexynilide gave an inseparable mixture of **14** and **15** (3:1; 58%). This is most likely due to the fact that deprotonation, but not epoxide formation, occurred resulting in displacement of the tosylate at C2 by the second equivalent of nucleophile. Conversely, reaction with **1** generated in situ gave ring opening at C1 (with complete inversion) as expected in 77% (**13**), whereas **14** and **15** were again obtained as an inseparable mixture, albeit with a slight change in regioselectivity (2:3).

Note: We speculate that the cuprate addition produces an inversion of stereochemistry (i.e. **13**), whereas the use of Grignard and organolithium reagents afforded racemized products (i.e. **9**, **11**, and **15**), because the copper can form a five-membered chelate with **1** preventing formation of a stabilized carbocation in the case of RLi and RMg.

Reactions with less-reactive anionic carbon nucleophiles like nitromethane, 1,3-cyclohexane-dione and bis(sulfonylphenyl)methane were not successful.

Reaction of **1** with D-(+)-α-methylbenzylamine gave an inseparable mixture of two stereoisomers **16** (60:40; 54%) indicating an S_N1 mechanism. Ethanethiol, however, gave a mixture of regioisomers (**17**:**18**, 1:3).

In conclusion, a facile route to in situ generated enantiomerically pure (*R*)-**1** and (*S*)-**2** 2-furyloxiranes has been established. Their use in synthesis has been further demonstrated and understood with nucleophilic ring-opening studies leading to a simple one-pot procedure without the need to handle these sensitive epoxides.

Acknowledgment

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References and Notes

(1) (a) Merten, J.; Fröhlich, R.; Metz, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 5991. (b) Merten, J.; Hennig, A.; Schwab, P.; Fröhlich, R.; Tokalov, S. V.; Gutzeit, H. O.; Metz, P. *Eur. J. Org. Chem.* **2006**, 1144.
(2) Hamada, T.; Torii, T.; Izawa, K.; Ikariya, T. *Tetrahedron* **2004**, *60*, 7411.
(3) (a) Hayashi, M.; Kawabata, H.; Yamada, K. *Chem. Commun.* **1999**, 965. (b) Babu, B. S.; Balasubramanian, K. K. *J. Org. Chem.* **2000**, *65*, 4198. (c) Agarwal, A.; Rani, S.; Vankar, Y. D. *J. Org. Chem.* **2004**, *69*, 6137. (d) Yadav, J. S.; Reddy, B. V. S.; Madhavi, A. V. *J. Mol. Catal. A: Chem.* **2005**, *226*, 213.
(4) Although D-glucal is commercially available for large-scale reactions, the use of the cheaper peracetyl derivative is recommended.
(5) Yamaguchi, Y.; Tatsuta, N.; Haykawa, K.; Kanematsu, K. *J. Chem. Soc., Chem. Commun.* **1989**, 470.
(6) **Synthesis of (*R*)-1-(Furan-2-yl)ethane-1,2-diol (3)**
A catalytic amount of NaOMe was added to a solution of **4** (5.44 g, 20 mmol) in MeOH (20 mL) and stirred for 4 h at r.t. After evaporation of the solvent the resulting syrup was dissolved in MeCN (20 mL) and $FeCl_3 \cdot 6H_2O$ (270 mg, 1 mmol) was added. Usually the reaction is complete within 1 h. The whole reaction mixture was subjected to column chromatography on silica (PE–EtOAc = 1:2, R_f = 0.3) to obtain 2.1 g (82%).
(7) **Synthesis of Compound 6**
To a solution of **3** (2.1 g, 16.3 mmol) in pyridine (20 mL) was added TsCl (3.83 g, 20.6 mmol) and the reaction mixture was stirred over night at r.t. The whole mixture was poured onto a slurry of ice (300 mL) and concd HCl (ca. 10 mL). The resulting mixture was extracted with Et_2O (200

mL) and the organic layer was washed with sat. $NaHCO_3$ solution (50 mL), H_2O (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated to approx. 60 mL. The so-prepared solution was used without further purification, but stored in the fridge over 4 Å MS (0.14 M); $[\alpha]_D^{20}$ +36.7 (*c* 4.01, Et_2O). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.79–7.75 (m, 2 H), 7.35–7.31 (m, 3 H), 6.32–6.30 (m, 2 H), 4.95 (dd, 1 H, *J* = 4.4, 7.0 Hz), 4.31–4.19 (m, 2 H), 2.65 (br s, OH), 2.44 (s, 3 H), ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.4, 145.1, 142.6, 132.5, 129.9, 128.0, 110.4, 107.9, 71.4, 65.9, 21.6 ppm. MS (ESI): *m/z* = 305 $[M + N]^+$. HRMS: *m/z* calcd for $C_{13}H_{14}NaO_5S$: 305.0460; found: 305.0467. Note: Tosylate **6** is stable in solution and on silica gel, however, if concentrated at elevated temperatures (40–50 °C) rapid polymerization occurs affording a dark-green gum. Analytical samples were obtained after column chromatography, concentration at 20 °C and finally evaporation of the remaining solvent under high vacuum. Compound **6** is stable under argon for several hours in pure form.

(8) For other 2-furyloxirane precursors, such as 2-chlorofuryl alcohols, sensitivity towards amines has been reported,[3a,9] whereas tosylate **6** is stable in the presence of benzylamine and even thioethane at r.t. as observed over 96 h.

(9) Tannis, S. P.; Evans, B. R.; Nieman, J. A.; Parker, T. T.; Taylor, W. D.; Heasley, S. E.; Herrinton, P. M.; Perrault, W. R.; Hohler, R. A.; Dolak, L. A.; Hester, M. R.; Seest, E. P. *Tetrahedron: Asymmetry* **2006**, *17*, 2154.

(10) Peracetylation with Ac_2O/pyridine, formation of the L-glucosyl bromide with HBr/AcOH followed by elimination with zinc dust achieved 53% overall yield. Following the procedure for L-galactal: (a) Litjens, R. E. J. N.; den Heeten, R.; Timmer, M. S. M.; Overkleeft, H. S.; van der Marel, G. A. *Chem. Eur. J.* **2005**, *11*, 1010. (b) Tri-*O*-acetyl-L-glucal: $[\alpha]_D^{20}$ +23.4 (*c* 1.01, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.45 (d, 1 H, *J* = 6.1 Hz), 5.34–5.30 (m, 1 H), 5.20 (t, 1 H, *J* = 6.5 Hz), 4.83 (dd, 1 H, *J* = 6.2, 3.2 Hz), 4.38 (dd, 1 H, *J* = 11.7, 6.2 Hz), 4.26–4.15 (m, 2 H), 2.08 (s, 3 H), 2.06 (s, 3 H), 2.03 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 170.2, 169.4, 145.5, 98.9, 73.8, 67.3, 67.1, 53.3, 20.8, 20.6, 20.6 ppm.

(11) (a) Alcaide, B.; Areces, P.; Borredon, E.; Biurrun, C.; Castells, J. P.; Plumet, J. *Heterocycles* **1990**, *31*, 1997. (b) Oh, K. B.; Cha, J. H.; Cho, Y. S.; Choi, K. I.; Koh, H. Y.; Chang, M. H.; Pae, A. N. *Tetrahedron Lett.* **2003**, *44*, 2911.

(12) (a) Alcaide, B.; Biurrun, C.; Plumet, J. *Tetrahedron* **1992**, *48*, 9719. (b) Sutowardoyo, K. I.; Emziane, M.; Lhoste, P.; Sinou, D. *Tetrahedron* **1991**, *47*, 1435.

(13) Smith, A. B. III; Xian, M. *J. Am. Chem. Soc.* **2006**, *128*, 66.

(14) **Representative Experimental Procedure and Characterization Data for Selected Compounds**
To a solution of **6** (5.0 mL, 0.71 mmol, 0.14 M) in Et_2O[7] was added NaH (2 equiv, 60 mg, 60% in mineral oil) under an argon atmosphere at r.t. After 30 min a solution of Li-TBS-dithiane[13] (1.2 equiv) in anhyd THF (2 mL) containing HMPA (0.7 mL) was added at r.t. The reaction was quenched after 2 h with sat. NH_4Cl solution (10 mL) and extracted with Et_2O (20 mL). The organic layer was washed with H_2O (10 mL), brine (10 mL), dried ($MgSO_4$), and evaporated. The residue was further purified by column chromatography on silica gel (PE–EtOAc, 50:1) affording **8** (122 mg, 50%; R_f = 0.5) and **9** (81 mg, 33%; R_f = 0.41).
Compound **8**: $[\alpha]_D^{20}$ +77.0 (*c* 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.32 (m, 1 H), 6.30–6.27 (m, 1 H), 6.19–6.17 (m, 1 H), 4.96 (dd, *J* = 8.9, 4.8 Hz, 1 H), 4.07 (dd, *J* = 9.3, 5.4 Hz, 1 H), 2.86–2.75 (m, 4 H), 2.34–2.23 (m, 1 H), 2.16–2.06 (m, 2 H), 1.94–1.84 (m, 1 H), 0.85 (s, 9 H), 0.06 (s, 3 H), –0.11 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.1, 141.6, 110.0, 106.3, 64.8, 43.4, 42.2, 30.1, 29.6, 26.0, 25.8, 18.2, –5.0, –5.2 ppm. ESI-MS: *m/z* = 367 $[M + Na^+]$. The ee determination by derivatization unfortunately resulted in elimination giving **19**.
Compound **9**: ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.34 (m, 1 H), 6.32–6.30 (m, 1 H), 6.24–6.22 (m, 1 H), 4.45 (d, *J* = 6.5 Hz, 1 H), 4.03 (dd, *J* = 9.9, 6.5 Hz, 1 H), 3.90 (dd, *J* = 9.9, 6.5 Hz, 1 H), 3.29 (td, *J* = 6.5, 6.5 Hz, 1 H), 2.88–2.82 (m, 4 H), 0.85 (s, 9 H), 0.02 (s, 3 H), –0.01 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.6, 141.3, 110.2, 108.1, 62.3, 48.6, 46.8, 30.7, 30.5, 29.7, 25.8, 18.2, –5.5 ppm. ESI-MS: *m/z* = 367 $[M + Na^+]$.
NMR Data of Selected Compounds
Compound **10**: $[\alpha]_D^{20}$ +15.5 (*c* 4.02, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.35 (m, 1 H), 6.32–6.30 (m, 1 H), 6.26–6.24 (m, 1 H), 5.01 (dd, *J* = 8.9, 4.6, 1 H), 4.17 (dd, *J* = 8.8, 5.8 Hz, 1 H), 2.91–2.78 (m, 4 H), 2.36–2.20 (m, 2 H), 2.15–2.05 (m, 2 H), 1.95–1.80 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.5, 142.3, 110.2, 106.3, 64.7, 43.3, 40.8, 29.9, 29.7, 25.9 ppm. ESI-MS: *m/z* = 253 $[M + Na^+]$.
Compound **13**: $[\alpha]_D^{20}$ –19.8 (*c* 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.32 (m, 1 H), 6.30–6.28 (m, 1 H), 6.09–6.07 (m, 1 H), 3.72 (br d, *J* = 6.2 Hz, 2 H), 2.87 (app quin, *J* = 5.4 Hz, 1 H), 1.65–1.57 (m, 2 H), 1.53 (br s, OH), 1.34–1.19 (m, 4 H), 0.85 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.3, 141.4, 110.0, 106.2, 65.2, 42.1, 29.7, 29.4, 22.6, 13.9 ppm.
Compound **18**: ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.36 (m, 1 H), 6.33–6.31 (m, 1 H), 6.24–6.22 (m, 1 H), 4.07–4.02 (m, 1 H), 4.00–3.91 (m, 1 H), 3.88–3.80 (m, 1 H), 2.56–2.44 (m, 2 H), 1.20 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.8, 142.3, 110.4, 107.4, 63.0, 45.6, 24.7, 14.8 ppm.

(15) The product from this reaction has been previously characterized; our data agree with the previously published: Blake, A. J.; Cunningham, A.; Ford, A.; Teat, S. J.; Woodward, S. *Chem. Eur. J.* **2000**, *6*, 3586.