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# Synthetic Research on Cyclitols Using $C_6$-Chiron, 6-(Benzyloxy)-3-cyclohexen-1-ol: A Concise and Highly Diastereoselective Synthesis of (–)-*gala*-Quercitol

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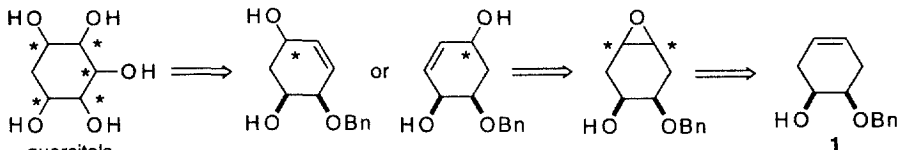
***Abstract:*** Transformation of a $C_6$-chiron, 6-(benzyloxy)-3-cyclohexen-1-ol into polyoxygenated cyclohexanes involving a stereodivergent epoxide rearrangement was investigated. An asymmetric synthesis of (–)-*gala*-quercitol was accomplished *via* sequential highly diastereoselective epoxidation, base-promoted epoxide rearrangement, and dihydroxylation. 

*Keywords:* $C_6$-Chiron; Cyclitols; Epoxide; Isomerization; *gala*-Quercitol

Stereocontrolled syntheses of cyclitols are of interest owing to their potent glycosidase inhibitory activity. The chiral pool approach utilizing naturally occurring products such as carbohydrates or cyclitols has limitations because of the restricted availability of chiral sources and often requires relatively many steps for manipulation of its functionality. On the other hand, asymmetric synthesis starting form easily accessible chiral templates would flexibly afford various cyclitols.[1] Our strategy is outlined in Scheme 1. A $C_6$-chiron, 6-(benzyloxy)-3-cyclohexen-1-ol **1** can be converted into quercitols *via* three diastereoselective reactions: 1) epoxidation, 2) isomerization to allylic alcohol, and 3) dihydroxylation. The key to this strategy is stereocontrol in each step, especially, the stereodivergent epoxide rearrangement based on conformational changes of the cyclohexane ring by switching the protection on the hydroxy group. In this paper, we describe a novel approach towards quercitols and a highly diastereoselective synthesis of (–)-*gala*-quercitol using the $C_6$-chiron **1**, which is readily obtained by asymmetric desymmetrization of *meso*-4-cyclohexene-1,2-diol.[2]




**Scheme 1 Retrosynthetic analysis of quercitols**

The epoxidation of **1** was first examined. MCPBA and magnesium monoperoxyphtalate (MMPP) epoxidation gave epoxides **2a** and **2b** in moderate to high yields, but the diastereoselectivity was low (entries 1 and 2). On the other hand, vanadyl acetylacetonate [$VO(acac)_2$] catalyzed epoxidation using *tert*-butyl hydroperoxide (TBHP) shows complete *syn*-selectivity by hydrogen bonding with the free alcohol to give the epoxide **2a** (entry 3). In contrast, dimethyldioxirane provided *anti*-epoxide **2b** as its sole product.[3] Thus, stereocontrol of epoxidation was perfectly achieved.[4]

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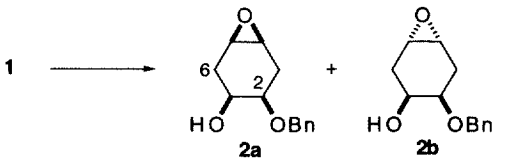



**Table 1.** Epoxidation of 6-(Benzyloxy)-3-cyclohexen-1-ol **1**[a]

| Entry | Conditions (equiv.) | Yield (%)[b] | **2a** : **2b**[c] |
|---|---|---|---|
| 1 | MCPBA (1.1), $CH_2Cl_2$, –78 ℃ to rt | 83 | 45 : 55 |
| 2 | MMPP (0.6), *i*-PrOH–$H_2O$ (1 : 1), rt | 64 | 42 : 58 |
| **3** | **TBHP (2.0), VO(acac)$_2$ (0.02), $CH_2Cl_2$, rt** | **79** | **100 : 0** |
| **4** | **dimethyldioxirane (4.5), ether, rt** | **78** | **0 : 100** |

[a] Racemic **1** was used. [b] Combined yield of **2a** and **2b**. [c] Determined by $^1$H-NMR spectroscopy.

Next, base-promoted isomerization of the epoxide **2a** to an allylic alcohol was examined (Table 2). Di-*n*-alkyl amides (entries 2–4) produced a higher yield than LDA (entry 1). These results were in accordance with those of Rickborn's report.[5] Schlosser's mixed base (sodium hydride/potassium *tert*-butoxide) caused decomposition (entry 5),[6] while the addition of HMPA improved the yield (entry 6). Interestingly, 1,3-diol **3a** was obtained exclusively in all entries.

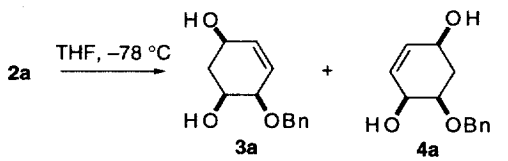



**Table 2.** Base-induced Isomerization of the *syn*-Epoxide **2a**[a]

| Entry | Conditions (equiv.) | Yield (%)[b] | **3a** : **4a**[c] |
|---|---|---|---|
| 1 | LDA (5), | 37 | 100 : 0 |
| 2 | *n*-$Bu_2NLi$ (5) | 45 | 100 : 0 |
| 3 | *n*-$Pr_2NLi$ (5) | 50 | 100 : 0 |
| 4 | $Et_2NLi$ (5) | 44 | 100 : 0 |
| 5 | *n*-$Bu_2NLi$ (5), *t*-BuOK (5) | decomp. | — |
| **6** | ***n*-$Pr_2$NLi (5), HMPA (5)** | **61** | **100 : 0** |

[a] Racemic **2a** was used. [b] Combined yield of **3a** and **4a**. [c] Determined by $^1$H-NMR spectroscopy.

This high regioselectivity is explained as follows: Thummel and Rickborn reported that the isomerization of epoxides proceeds *via syn*-β-hydrogen abstraction rather than *via anti*-one, where the metal of the base coordinates to the epoxide oxygen.[7,8] In the same process, the base would approach the epoxide in such a way that steric interaction with the axial substituent is minimized (Fig. 1). Thus, in the case that R is Li, the transition state A is expected to be favored more than the transition state B, since the size of the benzyl ether group is larger than that of lithium alkoxide, thereby affording the 1,3-diol **3a** exclusively. This hypothesis indicates that opposite selectivity would be expected if R is larger than benzyl ether and transition state B becomes more stable than transition state A. Therefore, we investigated the influence of the protecting group (R) on the regioselectivity of the epoxide rearrangement.

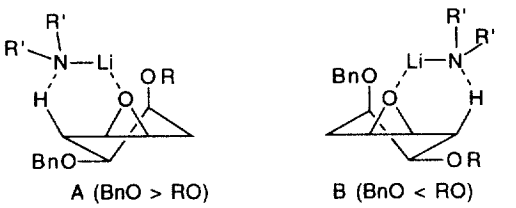



**Fig. 1** Plausible mechanism of regioselective isomerization of epoxides

The results are shown in Table 3. Methoxymethyl (MOM) ether **2c** showed moderate selectivity since MOM has a similar steric demand to the Bn group (entry 2). Epoxide **2d** with a large *tert*-butyldimethylsilyl group provided the reversed selectivity to give the 1,4-diol **4d** as a major product (entry 3), while only 1,4-diol **4e** was obtained from the pivalate **2e** (entry 4). Since the alcohol **4e** can be converted by deprotection into the 1,4-diol **4a**, stereocontrol of the epoxide opening was accomplished by switching the protection on the hydroxy group, and thus both diastereomeric isomers **3a** and **4a** are obtained with complete diastereoselectivity.[9,10]

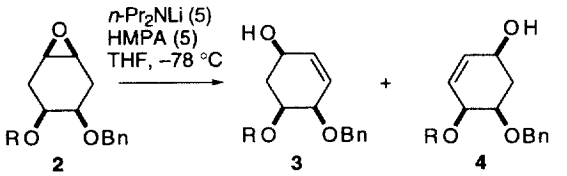
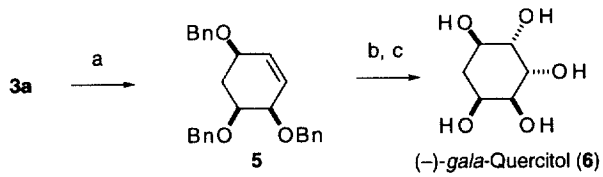



**Table 3.** Effect of Protecting Group (R) on Isomerization of **2**[a]

| Entry | Epoxide | R | Yield (%)[b] | **3** : **4**[c] |
|---|---|---|---|---|
| **1** | **2a** | **H** | **61** | **100 : 0** |
| 2 | **2c** | MOM | 90 | 76 : 24 |
| 3 | **2d** | TBS | 57 | 12 : 88 |
| **4** | **2e** | **Piv** | **89** | **0 : 100** |

[a] Racemic **2** was used. [b] Combined yield of **3** and **4**. [c] Determined by $^1$H-NMR spectroscopy.

*gala*-Quercitol (2-deoxy-*allo*-inositol) is one of the diastereomeric isomers of quercitol congeners in which ten diastereomeric isomers exist. Several syntheses have been reported[11] since it was synthesized in 1961 (D-form)[11a] and in 1982 (L-form).[11c] However, few spectral data were reported and one of the synthetic reports shows a different specific rotation from the others.[11e] We were interested in this compound as a synthetic target to elucidate its full data. The diol **3a** derived from (1*S*,2*R*)-**1** (>96% ee) into (–)-*gala*-quercitol (**6**), as shown in Scheme 2.




**Scheme 2** *Reagents and Conditions:* a) BnBr, NaH, *n*-$Bu_4NI$, THF, –78 °C→ rt (83%); b) cat. $OsO_4$, NMO, acetone–water (30 : 1), rt; c) $H_2$, $Pd(OH)_2$–C, MeOH, 3 atm, rt (91% in 2 steps) .

The 1,3-diol **3a** was protected as a tribenzyl ether with NaH and BnBr in the presence of *n*-$Bu_4NI$. Dihydroxylation of the resulting **5** with a catalytic amount of $OsO_4$ with 4-methylmorphorine *N*-oxide as a co-oxidant followed by debenzylation using Pd–C under 3 atm of hydrogen atmosphere gave the expected (–)-*gala*-quercitol **6** as a single isomer, whose physical and spectral properties[12] fully agreed with the reported value.[11a,b,d]

In conclusion, a highly diastereoselective total synthesis of (–)-*gala*-quercitol was accomplished in short steps (overall yield 36%, 5 steps from **1**) starting from the $C_6$-chiron **1** *via* sequential reactions of diastereoselective epoxidation, isomerization of epoxide, and dihydroxylation. Since both epoxidation and epoxide rearrangement proceed with complete stereocontrol, this methodology would also be versatile for asymmetric synthesis of other quercitols and their congeners. Syntheses of other cyclitols using this strategy are currently under investigation.

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## References and Notes

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4. Stereochemistries of isomers **3a** and **3b** were confirmed by low field shift of the signals due to protons *syn* to the epoxide in $^1$H-NMR spectroscopic data [$\Delta\delta$ *anti–syn* +0.19 (2-H), –0.28 (6-H$\beta$), +0.22 (6-H$\alpha$)].
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9. The structures of **4** and **5** were established on the basis of COSY.
10. Base-promoted epoxide opening of the *anti*-epoxide **2b** proceeded with lower selectivity. We succeeded in improving the regioselectivity of the isomerization of **2b** by epoxide opening with phenylselenide and the subsequent elimination of phenylselenoxide. The results will be reported elswhere.
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12. **Data of (–)-*gala*-quercitol (6):** Mp. 257–258 °C (from MeOH–$Et_2O$). $[\alpha]_D^{25}$ –49.6 (*c* 0.30, $H_2O$). $^1$H-NMR (500 MHz, $D_2O$) $\delta$: 1.53 (dt, 1H, *J*=12.2, 11.0 Hz, 6-H$\beta$), 1.81 (dt, 1H, *J*=12.2, 4.3 Hz, 6-H$\alpha$), 3.48 (dd, 1H, *J*=9.2, 2.4 Hz, 4-H), 3.60 (ddd, 1H, *J*=11.0, 9.2, 4.3 Hz, 5-H), 3.73 (t, 1H, *J*=3.7 Hz, 2-H), 3.80–3.84 (m, 2H, 1- and 3-H). $^{13}$C-NMR (67.8 Hz, $D_2O$) $\delta$: 34.26 (C6), 67.05 (C1), 68.55 (C5), 72.42 (C3), 72.63 (C2), 72.88 (C4). IR (KBr, cm$^{-1}$) 3313, 2937, 1063, 660. Mass (FAB) 165 ($M^+$+H). HR-MS (FAB) Calcd for $C_6H_{12}O_5$+H 165.0762. Found 165.0754.