# Improvement of Diastereoselectivity in Oxyselenenylation of Cyclohexene with (*R*,*R*)-Hydrobenzoin Employing Chiral Selenium and Achiral Methylselenium Electrophiles

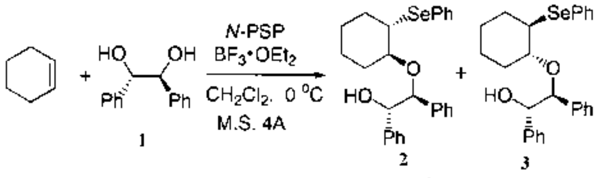
**Kwan Soo Kim,* Choong Woon Moon, Jung Keun Hong, and Jin Hwan Kim**

*Department of Chemistry, Yonsei University, Seoul 120-749, Korea*

*Received November 11, 2000*

**Keywords :** (*R*,*R*)-Hydrobenzoin, Chiral selenium reagents, Asymmetric oxyselenenylation, (*R*,*R*)-1,2-Dinaphthalenylethan-1,2-diol.

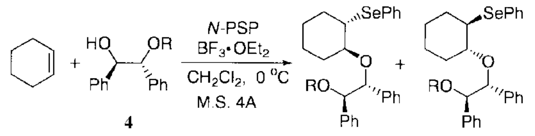
We reported previously the synthesis of physiologically important D-*chiro*-inositol and *muco*-quercitol mediated by the sequential oxyselenenylation of cyclohexene.[1] The first step of our methodology was the oxyselenenylation of cyclohexene with (*S*,*S*)-hydrobenzoin (**1**) and *N*-(phenylseleno)phthalimide (*N*-PSP) in the presence of $BF_3 \cdot OEt_2$ and afforded an equal amount of diastereomeric oxyselenides **2** and **3** (Scheme 1). In order to improve the diastereoselectivity of the first step of the sequence and in the hope of gaining an insight into the factors affecting the diastereoselectivity in the oxyselenenylation of cyclohexene, we have conducted the oxyselenenylations of cyclohexene employing modified hydrobenzoins with the phenylselenium reagent, employing (*R*,*R*)-hydrobenzoin with new electrophilic chiral selenium reagents, and employing (*R*,*R*)-hydrobenzoin with a methylselenium reagent. Although there have been many reports on the asymmetric oxyselenenylation of the achiral olefin with various chiral selenium reagents,[2-5] few results are known for the asymmetric oxyselenenylation of the achiral olefin with the chiral alcohol.[6]



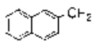
**Scheme 1**

Modified (*R*,*R*)-hydrobenzoins were prepared by the protection of one of two hydroxyl groups in (*R*,*R*)-hydrobenzoin (**4a**). Oxyselenenylation of cyclohexene with each of these mono-protected hydrobenzoins was carried out employing a phenylselenium reagent, *N*-PSP in the presence of $BF_3 \cdot OEt_2$ and molecular sieves to provided a mixture of two diastereomeric oxyselenides **5** and **6** as shown in Table 1.[7] Modified (*R*,*R*)-hydrobenzoins **4b** and **4c** showed somewhat improved diastereoselectivities (entries 2 and 3) but compounds **4d**, **4e**, and **4f** showed virtually no diastereoselectivities (Entries 4-6).[8]

**Table 1**. Oxyselenenylation of Cyclohexene with Mono-protected (*R*,*R*)-Hydrobenzoins



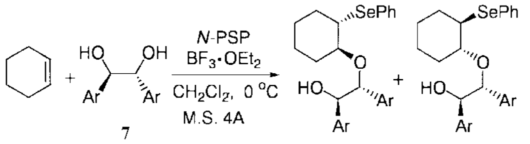
**4** **5** **6**

| Entry | Alcohol | R of **4** | Products | Product Ratio (**5**/**6**) | Yield (%) |
|---|---|---|---|---|---|
| 1 | **4a** | H | **5a/6a** | 50:50 | 80 |
| 2 | **4b** | Bn | **5b/6b** | 69:31[a] | 82 |
| 3 | **4c** | $Ph_3Si$ | **5c/6c** | 62:38 | 50[b] |
| 4 | **4d** | Bz | **5d/6d** | 49:51 | 55[c] |
| 5 | **4e** |  | **5e/6e** | 49:51 | 44[d] |
| 6 | **4f** | $C_6H_{13}CO$ | **5f/6f** | 50:50 | 74 |

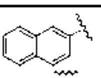
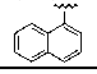
[a] Ratio determined by GC and NMR. [b] Isolated yield after deprotection with $Bu_4NF$. [c] Isolated yield after deprotection with $NaOH/H_2O$. [d] Isolated yield after deprotection with DDQ.

Instead of mono-protected (*R*,*R*)-hydrobenzoins, (*R*,*R*)-1,2-dinaphthalenylethan-1,2-diols **7a** and **7b**, prepared by the known procedure,[9] were employed for the oxyselenenylation of cyclohexene as shown in Table 2. Diol **7a** showed a low selectivity (64 : 36), whereas the diol **7b** did not exhibited any selectivity at all. The absolute stereochemistry of the major product **8a** was determined by comparison with authentic 1,2,3-cyclohexanetriol[10] after a few transformations of **8a** into the corresponding triol.[11] The results shown in Tables 1 and 2, however, indicated that the modification of hydrobenzoin would not be the way to improve the di-

**Table 2**. Oxyselenenylation of Cyclohexene with (*R*,*R*)-1,2-Dinaphthalenyethan-1,2-diols



**7** **8** **9**

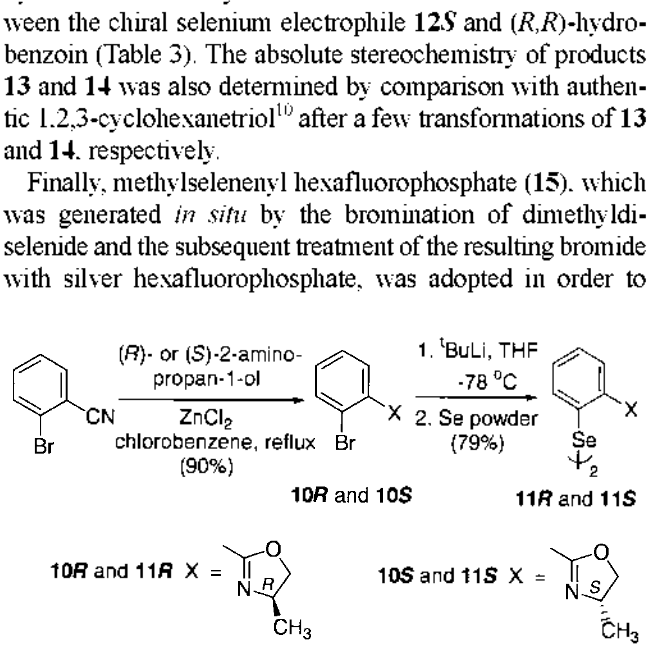
| Diols | Ar | Products | Ratio | Yield (%)[a] |
|---|---|---|---|---|
| **7a** |  | **8a/9a** | 64:36 | 62 |
| **7b** |  | **8b/9b** | 50:50 | 54 |

[a] Isolated yields

astereoselectivity in the oxyselenenylation of cyclohexene.[12]

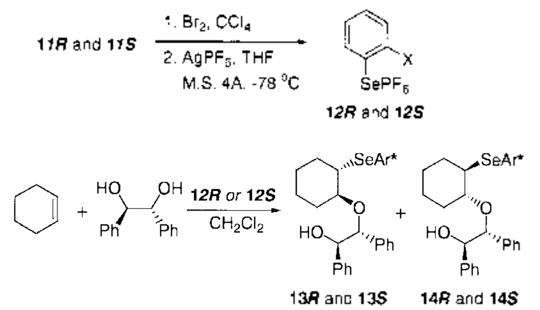
New chiral selenium electrophiles possessing a chiral oxazoline auxiliary were, in turn, devised for the oxyselenenylation of cyclohexene. Chiral bromides **10*R*** and **10*S***, obtained from 2-bromobenzonitrile with (*R*)- and (*S*)-2-aminopropan-1-ol, were transformed to chiral diselenides **11*R*** and **11*S***, respectively, as shown in Scheme 2. Oxyselenenylations of cyclohexene with chiral selenenyl hexafluorophosphates **12R** and **12S**, generated *in situ* from **11*R*** and **11*S***, were carried out in combination with (*R*,*R*)-hydrobenzoin. The chiral selenium reagent **12*S*** containing (*S*)-methyloxazoline moiety exhibited a higher selectivity (79 : 21) than its enantiomer **12*R***. This suggests that the diastereoselectivity was enhanced by the double stereodifferentiation between the chiral selenium electrophile **12*S*** and (*R*,*R*)-hydrobenzoin (Table 3). The absolute stereochemistry of products **13** and **14** was also determined by comparison with authentic 1,2,3-cyclohexanetriol[10] after a few transformations of **13** and **14**, respectively.

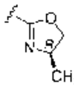
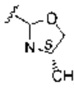
Finally, methylselenenyl hexafluorophosphate (**15**), which was generated *in situ* by the bromination of dimethyldiselenide and the subsequent treatment of the resulting bromide with silver hexafluorophosphate, was adopted in order to investigate the diastereoselectivity of the oxyselenenylation. Surprisingly, the reaction of cyclohexene employing (*R*,*R*)-hydrobenzoin and the methylselenium electrophile **15** led to the highest diastereoselectivity (85 : 15) in a reasonable yield as shown in Scheme 3. The origin of the drastic increase in the diastereoselectivity of this reaction employing methylselenium hexafluorophosphate **15** compared with that employing phenylselenium electrophiles and even compared with that employing chiral selenium reagents is unclear as yet. When other methylselenium electrophiles with different counteranions, such as methylselenenyl bromide and methylselenenyl triflate, the oxyselenenylations with (*R*,*R*)-hydrobenzoin proceeded with poor yields but with almost same diastereoselectivities. Oxyselenenylation of cyclohexene employing the electrophile **15** and the modified hydrobenzoins **4** also gave poor results. The fact that the high diastereoselectivity was achieved employing the methylselenium reagent and (*R*,*R*)-hydrobenzoin has a significant practical value. Unlike chiral selenium reagents and modified hydrobenzoins, the methylselenenyl hexafluorophosphate and (*R*,*R*)-hydrobenzoin are readily available reagents.



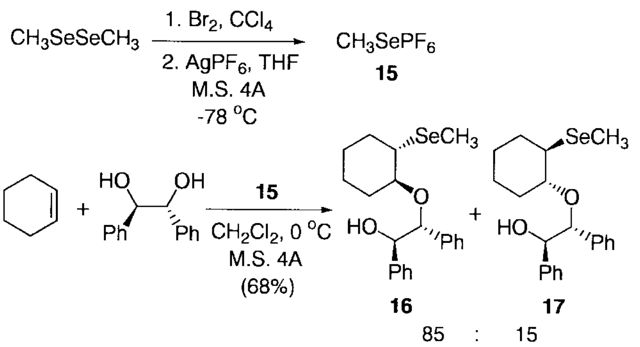
Scheme 2

**Table 3.** Oxyselenenylation of Cyclohexene with Chiral Selenium Reagents



| Ar*SePF$_6$ | X of **12** | Products | Product Ratio (13/14) | Yield (%)[a] |
|---|---|---|---|---|
| **12*R*** |  | **13*R*/14*R*** | 64:36 | 58 |
| **12*S*** |  | **13*S*/14*S*** | 79:21 | 43 |

[a]Isolated yields



Scheme 3

In conclusion, a little or no enhancement of the diastereoselectivity was observed when modified (*R*,*R*)-hydrobenzoins and the phenylselenium electrophile were employed in the oxyselenenylation of cyclohexene. With the new chiral selenium reagent **12S** and (*R*,*R*)-hydrobenzoin, on the other hand, the oxyselenenylation proceeded with a substantially higher diastereoselectivity (79:21) by the double stereodifferentiation. Surprisingly, the highest diastereoselectivity (85 : 15) was observed in the reaction with methylselenenyl hexafluorophosphate **15** and (*R*,*R*)-hydrobenzoin.

## Experimental Section

**Synthesis of Chiral Diselenide 11*R*.** To a solution of the bromide **10*R*** (440 mg, 1.83 mmol) and TMEDA (227 μL, 1.83 mmol) in THF (5 mL) was slowly added *t*-BuLi (1.7 M in pentane, 2.05 mL, 3.48 mmol) at 78 °C and the solution was stirred for 20 min. Selenium powder (217 mg, 2.75 mmol) was added portionwise. The mixture was allowed to warm up to room temperature and stirred for an additional 3 h. After oxygen had been bubbled through the reaction mixture overnight, it was diluted with EtOAc, washed with NaHCO$_3$, and water. The dried organic phase was evaporated under vacuum and the residue was purified by flash chromatography on silica gel eluted with hexane/ethyl acetate (4/1) to yield **11*R*** (346 mg, 79%) as yellow solids: mp 137-138 °C; $[\alpha]_D$= +79.2 (*c* 0.5 in $CHCl_3$); $^1H$ NMR ($CDCl_3$, 250 MHz) $\delta$ 1.44 (d, *J* = 6.3 Hz, 3H), 3.96-4.06 (m, 1H), 4.51-4.65 (m, 2H), 7.21-7.25 (m, 2H), 7.81-7.86 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 63 MHz) $\delta$ 21.9, 62.6, 74.0, 125.8, 126.3, 130.0, 130.6, 131.4, 133.3, 163.1; IR (KBr) 1637 $cm^{-1}$. Anal. Calcd for $C_{20}H_{20}O_2N_2Se_2$: C, 50.22; H, 4.22; N, 5.86. Found: C, 50.23; H, 4.21; N, 5.81.

**Oxyselenenylation of Cyclohexene with Chiral Selenium Reagent 12*R* and (*R,R*)-Hydrobenzoin**. To a solution the diselenide **11*R*** (136 mg, 0.28 mmol) in $CCl_4$ (2 mL) in the presence of 4A molecular sieves was added slowly bromine (33 $\mu$L, 0.63 mmol) and the solution was stirred for 30 min at room temperature. After removal of the solvent under vacuum, a THF solution (1 mL) of $AgPF_6$ (165 mg, 0.65 mmol) was added to the residue at -78 °C and the mixture was stirred for further 30 min at -78 °C. To this solution of *in situ* generated **12*R***, was added a solution of (*R,R*)-hydrobenzoin (146 mg, 0.68 mmol) and cyclohexene (288 $\mu$L, 2.84 mmol) in $CH_2Cl_2$ (2 mL) at -78 °C and the solution was allowed to warm up to room temperature and stirred for an additional 5 h. The reaction mixture was partitioned between $CH_2Cl_2$ and saturated aqueous $NaHCO_3$ solution and the organic phase was washed with water and dried under vacuum. Flash column chromatography of the residue afforded oxyselenides **13*R*** (56 mg, 37%), $R_f$ 0.30 (hexane-ethyl acetate, 5/2) and **14*R*** (32 mg, 21%), $R_f$ 0.25 (hexane-ethyl acetate, 5/2).

Oxyselenide **13*R***: mp 115-116 °C; $[\alpha]_D$= +52.7 (*c* 1.3 in $CHCl_3$); $^1H$ NMR ($CDCl_3$, 250 MHz) $\delta$ 1.41 (d, *J* = 6.3 Hz, 3H), 1.55-2.10 (m, 8H), 3.38-3.66 (m, 3H), 3.94 (m, 1H), 4.30 (d, *J* = 8.4 Hz, 1H), 4.43-4.55 (m, 2H), 4.52 (d, *J* = 8.4 Hz, 1H), 6.92-7.77 (m, 14H); $^{13}C$ NMR ($CDCl_3$, 63 MHz) $\delta$ 21.8, 23.8, 26.0, 26.6, 33.5, 46.9, 62.7, 70.4, 73.8, 79.7, 88.1, 125.5, 127.5, 127.7, 127.9, 128.1, 128.8, 130.4, 130.44, 130.8, 134.3, 139.5, 139.9, 163.1; IR (KBr) 3456, 1646 $cm^{-1}$. Anal. Calcd for $C_{30}H_{33}O_3NSe$: C, 67.41; H, 6.22; N, 2.62. Found: C, 67.84; H, 6.17; N, 2.53.

Oxyselenide **14*R***: mp 109-111 °C; $[\alpha]_D$= +5.82 (*c* 0.6 in $CHCl_3$); $^1H$ NMR ($CDCl_3$, 250 MHz) $\delta$ 1.39 (d, *J* = 6.3 Hz, 3H), 1.55-2.20 (m, 8H), 3.42-3.53 (m, 3H), 3.92 (m, 1H), 4.35 (d, *J* = 8.1 Hz, 1H), 4.45-4.51 (m, 2H), 4.54 (d, *J* = 8.1 Hz, 1H), 6.98-7.69 (m, 14H); $^{13}C$ NMR ($CDCl_3$, 63 MHz) $\delta$ 21.7, 23.7, 25.9, 26.5, 33.4, 46.8, 62.6, 70.2, 73.6, 79.6, 88.0, 125.4, 127.35, 127.4, 127.5, 127.6, 127.7, 128.0, 128.7, 130.29, 130.3, 130.7, 134.2, 139.4, 139.8, 163.0; IR (KBr) 3440, 1645 $cm^{-1}$. Anal. Calcd for $C_{30}H_{33}O_3NSe$: C, 67.41; H, 6.22; N, 2.62. Found: C, 67.32; H, 6.48; N, 2.13.

**Oxyselenenylation of Cyclohexene with Chiral Diselenide 12*S* and (*R,R*)-Hydrobenzoin**. Reaction was conducted under the same condition as that with **11*R*** as described above to provide oxyselenides **13*S*** (51 mg, 34%), $R_f$ 0.65 (hexane-ethyl acetate, 1/1), and **14*S*** (14 mg, 9%), $R_f$ 0.60 (hexane-ethyl acetate, 1/1) as oils.

Oxyselenide **13*S***: $[\alpha]_D$= +22.5 (*c* 0.2 in $CHCl_3$); $^1H$ NMR ($CDCl_3$, 250 MHz) $\delta$ 1.40 (d, *J* = 6.4 Hz, 3H), 1.61-1.84 (m, 6H), 2.00-2.34 (m, 2H), 3.40-3.70 (m, 2H), 3.92 (m, 1H), 4.19 (brs, 1H), 4.29 (d, *J* = 8.4 Hz, 1H), 4.47-4.51 (m, 3H), 6.90-7.75 (m, 14H); IR (KBr) 3452, 1645 $cm^{-1}$.

Oxyselenide **14*S***: $[\alpha]_D$= +4.8 (*c* 0.13 in $CHCl_3$); $^1H$ NMR ($CDCl_3$, 250 MHz) $\delta$ 1.39 (d, *J* = 6.1 Hz, 3H), 1.51-1.78 (m, 6H), 1.95-2.30 (m, 2H), 2.82 (brs, 1H), 3.45-3.51 (m, 2H), 3.94 (m, 1H), 4.36 (d, *J* = 8.1 Hz, 1H), 4.45-4.49 (m, 2H), 4.53 (d, *J* = 8.1 Hz, 1H) 7.00-7.70 (m, 14H); IR (KBr) 3452, 1612 $cm^{-1}$.

**Oxyselenenylation of Cyclohexene with Methylselenium Reagent 15 and (*R,R*)-Hydrobenzoin**. To a solution the dimethyldiselenide (71 mL, 0.75 mmol) in $CCl_4$ (10 mL) in the presence of 4A molecular sieves was added slowly bromine (54 $\mu$L, 1.05 mmol) and the solution was stirred for 30 min at room temperature. After removal of the solvent under vacuum, a THF solution (5 mL) of $AgPF_6$ (472 mg, 1.87 mmol) was added to the residue at 78 °C and the mixture was stirred for further 30 min at 78 °C. To this solution of *in situ* generated **15**, was added a solution of (*R,R*)-hydrobenzoin (400 mg, 1.87 mmol) and cyclohexene (378 $\mu$L, 3.73 mmol) in $CH_2Cl_2$ (5 mL) at 78 °C and the solution was allowed to warm up to room temperature and stirred for an additional 7 h. The reaction mixture was partitioned between $CH_2Cl_2$ and saturated aqueous $NaHCO_3$ solution and the organic phase was washed with water and dried under vacuum. Flash column chromatography of the residue afforded oxyselenides **16** (151 mg, 58%) as white crystals, $R_f$ 0.45 (hexane-ethyl acetate, 4/1) and **17** (26 mg, 10%) as colorless oils, $R_f$ 0.35 (hexane-ethyl acetate, 4/1).

Oxyselenide **16**: mp 98-100 °C; $[\alpha]_D$= +46.7 (*c* 0.39 in $CHCl_3$); $^1H$ NMR ($CDCl_3$, 250 MHz) $\delta$ 1.04-1.19 (m, 3H), 1.53-1.69 (m, 4H), 2.13 (s, 3H), 2.15-2.21 (m, 1H), 2.79-2.89 (m, 1H), 3.38-3.47 (m, 1H), 3.65 (brs, 1H), 4.23 (d, *J* = 8.6 Hz, 1H), 4.69 (d, *J* = 8.6 Hz, 1H), 6.93-7.15 (m, 10H); $^{13}C$ NMR ($CDCl_3$, 63 MHz) $\delta$ 3.3, 24.3, 26.4, 33.1, 34.0, 45.7, 80.3, 83.5, 89.0, 127.5, 127.6, 127.7, 127.8, 128.6, 129.0, 139.3, 140.1; IR (KBr) 3408 $cm^{-1}$. Anal. Calcd for $C_{21}H_{26}O_2Se$: C, 64.77; H, 6.77. Found: C, 65.33; H, 6.83.

Oxyselenide **17**: $[\alpha]_D$= -13.8 (*c* 0.55 in $CHCl_3$); $^1H$ NMR ($CDCl_3$, 250 MHz) $\delta$ 1.26-1.42 (m, 5H), 1.60-1.75 (m, 1H), 1.89 (s, 3H), 2.13-2.17 (m, 2H), 2.83-2.92 (m, 1H), 3.26-3.43 (m, 1H), 3.60 (brs, 1H), 4.42 (d, *J* = 8.1 Hz, 1H), 4.70 (d, *J* = 8.1 Hz, 1H), 7.02-7.26 (m, 10H); $^{13}C$ NMR ($CDCl_3$, 63 MHz) $\delta$ 3.5, 23.4, 25.6, 29.8, 31.5, 44.0, 77.5, 78.6, 83.9, 127.4, 127.7, 127.9, 128.1, 128.2, 128.5, 137.6, 139.5; IR (NaCl) 3439 $cm^{-1}$. Anal. Calcd for $C_{21}H_{26}O_2Se$: C, 64.77; H, 6.77. Found: C, 64.77; H, 6.74.

**Acknowledgment**. This research was supported by a grant from Yonsei University (99034) and by Korea Research Foundation Grant (KRF-2000-DP0266). CWM was a research associate of the Basic Science Institute of Yonsei University.

## References and Notes

1. Kim, K. S.; Park, J. I.; Moon, H. K.; Yi, H. *J. Chem. Soc.*,

*Chem. Commun.* **1998**, 1945.

2. For a recent review of organoselenium chemistry in stereoselective reactions, see: Wirth, T. *Angew. Chem. Int. Ed.* **2000**, *39*, 3740.
3. For a recent review of chiral selenium compounds, see: Wirth, T. *Tetrahedron* **1999**, *55*, 1.
4. For a review of asymmetric oxyselenenylation, see: Fujita, K. *Reviews on Heteroatom Chemistry* **1997**, *16*, 101.
5. For a theoretical study on the origin of stereoselectivity in asymmetric oxyselenenylation, see Wang, X.; Houk, K. N.; Spichty, M.; Wirth, T. *J. Am. Chem. Soc.* **1999**, *121*, 8567.
6. For an example of oxyselenenylation with chiral nucleophiles, see: Fujita, K.; Iwaoka, M.; Tomoda, S. *Chem. Lett.* **1992**, 1123.
7. The diastereoselectivities of the reactions with other phenylselenium reagents such as phenylselenenyl chloride, phenylselenenyl bromide, phenylselenenyl triflate, and phenylselenenyl hexafluorophosphate were almost same but the yields were much lower than those with *N*-PSP.
8. The stereochemistry of the resulting oxyselenides **5** and **6** was, after removal of the protecting group, determined by the comparison with oxyselenides **5a** and **6a**, which had been already identified during our syntheses of *muco*-quercitol and D-*chiro*-inositol (see Ref. 1).
9. Rosini, C.; Scamuzzi, S.; Uccello-Barretta, G.; Salvadori, P. *J. Org. Chem.* **1994**, *59*, 7395.
10. Paulsen, H.; Brauer, O. *Chem. Ber.* **1997**, *110*, 331.
11. To get 1,2,3-cyclohexanetriol, oxyselenide **8a** was subject to the following transformations: i) oxidation/*syn*-elimination; ii) dihydroxylation with $OsO_4$; iii) hydrogenolysis with $H_2$.
12. Oxyselenenylations employing several other mono-protected (*R*,*R*)-hydrobenzoins, which were not listed in Table 1, were found to be no practical value because of very low yields.