Transformation of cyclohexene to enantiopure cyclitols mediated by sequential oxyselenenylation with (*S*,*S*)-hydrobenzoin: synthesis of D-*chiro*-inositol and *muco*-quercitol

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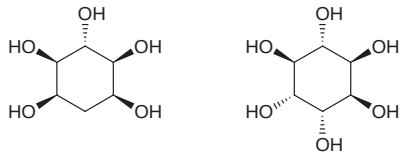
Oxyselenenylation of cyclohexene with (*S*,*S*)-hydrobenzoin and subsequent oxidation-elimination allows isolation of an allylic ether in which further phenylselenenylation is completely regioselective, thus allowing entry to the cyclitols D-*chiro*-inositol and *muco*-quercitol.

Cyclitols have attracted a great deal of attention from synthetic chemists due to their diverse biological activity and their versatility as synthetic intermediates.[1] Although several methods are available for the synthesis of cyclitol derivatives, there still remains a need for new methodology starting from simple starting materials because the cyclitol derivatives are structurally very diverse and the new methodology could be applied for the synthesis of other highly functionalized cyclic compounds. In this regard, it is noteworthy that cyclohexadiene *cis*-diols obtained from halobenzene by microbial oxidation[2] and from $PhMe_2SiCl$ by reduction and subsequent asymmetric dihydroxylation[3] have been used for the synthesis of cyclitols and other natural products.

Oxyselenenylation of a cycloalkene with an appropriate alcohol and the subsequent oxidation-elimination of the resultant oxyselenide would afford a cyclic allylic alcohol derivative. If a second oxyselenenylation of this cyclic allylic alcohol derivative was followed by oxidation-elimination to give a cycloalk-3-ene-1,2-diol derivative, a correctly protected cyclitol might be efficiently synthesized. However, it has been documented that the oxyselenenylation of both cyclic[4] and acyclic[5] allylic alcohol derivatives usually provides 1,3-diol rather than 1,2-diol derivatives. Therefore, in order to make this serial oxyselenenylation methodology work for the synthesis of enantiopure cyclitols, not only the stereochemistry but also the regiochemistry of the oxyselenenylation must be controlled. We have solved this problem by using a chiral diol, (*S*,*S*)-hydrobenzoin, for the oxyselenenylation of cyclohexene. Herein we report the successful conversion of cyclohexene into various enantiopure cyclitols and the synthesis of important natural cyclitols *muco*-quercitol **1** and D-*chiro*-inositol **2**, which

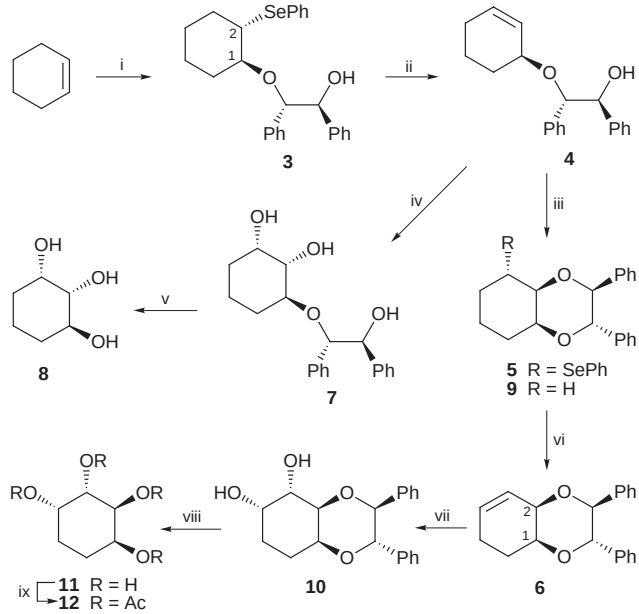


1 **2**

is valuable due to its physiological activity as an insulin mediator[6] and its limited availability.

To a solution of *N*-(phenylseleno)phthalimide (*N*-PSP) (3.44 mmol), (*S*,*S*)-hydrobenzoin (4.13 mmol), and cyclohexene (4.13 mmol) in CH_2Cl_2 (60 ml) was added slowly $BF_3{\cdot}OEt_2$ (0.34 mmol) at 0 °C. Stirring the reaction mixture at room temperature for a further 2 h afforded two diastereomeric oxyselenides [**3** plus the (1*R*,2*R*)-diastereomer; *ca.* 1:1 ratio] in 80% yield (Scheme 1). Although oxyselenenylation with other selenium reagents such as PhSeCl, PhSeBr and PhSeOTf was also possible, they frequently generated the undesired haloselenide or hydroxyselenide. Oxyselenide **3**‡ was separated by column chromatography and converted into olefin **4** {$[\alpha]_D$ −82.3 (*c* 0.7)} by the oxidation with $NaIO_4$ in the presence of $NaHCO_3$ followed by elimination of the resulting selenoxide. Intramolecular oxyselenenylation of **4** using PhSeOTf§ at −78 °C gave only *cis*-fused bicyclic dioxane **5**{$[\alpha]_D$ −34.5 (*c* 0.4)}. Thus, both regiochemistry and stereochemistry were completely controlled in the second oxyselenenylation step. Oxidation of selenide **5** and subsequent elimination provided olefin **6**.

Dihydroxylation of **4** with OsO_4 and NMO and subsequent hydrogenolysis of the resulting **7** afforded triol **8**. The absolute configuration of **8** was assigned on the basis of its ^1H NMR spectrum and by comparison of its specific rotation with that of authentic material {$[\alpha]_D$ +72.8 (*c* 1.0)}.[7] Reduction of selenide **5** with Bu_3SnH gave compound **9**. Dihydroxylation of **6** and subsequent hydrogenolysis of the resulting diol **10** gave tetrol **11**, which, by acetylation, afforded tetraacetate **12**. Examination of ^1H NMR spectrum of **9** and comparison with the ^1H NMR spectra of **12** with that of its known racemate[8] clearly indicated that the relative stereochemistry of compound **6** is *cis*. Consequently, the C1 and C2 configurations of cyclohex-3-ene-



Scheme 1 *Reagents and conditions*: i, (*S*,*S*)-hydrobenzoin, *N*-PSP, $BF_3{\cdot}OEt_2$ (cat.), CH_2Cl_2, room temp., 2 h, 40% of **3** and 40% of its (1*R*,2*R*)-diastereomer; ii, $NaIO_4$, $NaHCO_3$, MeOH–H_2O, room temp., 10 min, then 90 °C 48 h, 92%; iii, PhSeOTf, CH_2Cl_2, −78 °C, 2 h, 68%; iv, OsO_4 (cat.), NMO, acetone–H_2O, room temp., 24 h, 76%; v, H_2, Pd-C (cat.), EtOH, 50 psi, room temp., 12 h, 85%; vi, $NaIO_4$, $NaHCO_3$, MeOH–H_2O, room temp., 10 min, then 90 °C 48 h, 90%; vii, $K_2OsO_4H_2O$ (cat.), NMO, acetone–H_2O, reflux, 20 h, 92%; viii, H_2, Pd-C (cat.), EtOH, 50 psi, room temp., 8 h, 98%; ix, Ac_2O, pyridine, 50 °C, 12 h, 86%

1,2-diol derivative **6** were unambiguously determined to be *S* and *R*, respectively. On the other hand, a ^{1}H NMR decoupling experiment with compound **3** showed *trans* diaxial coupling (8.2 Hz) between H1 and H2 and thus the C1 and C2 configurations of **3** were assigned as *S* and *S*, respectively.

Epoxidation of **6** with MCPBA in CH_2Cl_2 afforded *trans*-epoxide **13** {R_f = 0.30 (silica gel, hexane−EtOAc, 10:1); $[\alpha]_D$ −126.9 (*c* 0.11)} along with its *cis* isomer {R_f = 0.11, $[\alpha]_D$ −112.0 (*c* 0.1)} (*trans*:*cis* = *ca.* 7:3) (Scheme 2). Epoxidation in other solvents gave poorer results. Diaxial opening of the epoxide ring of **13** with PhSeNa gave exclusively hydroxyselenide **14**, whereupon oxidation with 30% H_2O_2 followed by elimination provided allylic alcohol **15** {$[\alpha]_D$ + 3.0 (*c* 0.2)}. Dihydroxylation of **15** occurred on the opposite face to the allylic hydroxy group to afford exclusively triol **16** {$[\alpha]_D$ −50.5 (*c* 0.11)} in 92% yield. Hydrogenolysis of **16** provided *muco*-quercitol **1**, of which the spectroscopic data and physical properties were identical with those of authentic material. Further characterization of **1** was performed *via* transformation to the known pentaacetate **17**.[9]

Protection of the hydroxy group in **15** with the sterically demanding TBDPS group and subsequent epoxidation of the resulting TBDPS ether **18** {$[\alpha]_D$ +17.8 (*c* 1.1)} with MCPBA afforded the desired *trans*-epoxide **19** {R_f = 0.40 (silica gel, hexane–$CHCl_3$–EtOAc, 20:5:1); $[\alpha]_D$ −22.3 (*c* 0.74)} along with *cis*-epoxide {R_f = 0.35; $[\alpha]_D$ −33.2 (*c* 0.80)} (*trans*:*cis* = 3:2). Diaxial opening of the epoxide ring in **19** with PhSeNa afforded exclusively hydroxyselenide **20**, which turned out to be a mixture of two rotational isomers (3:2) about one of the single bonds in the OTBDPS group. The mixture of two stable atropisomers **20** was separated by flash chromatography, and each was converted into allylic alcohol **21,** which was also a stable and separable mixture of atropisomers (3:2). Evidence for the atropisomerism in compounds **20** and **21** could be readily obtained by removal of their TBDPS groups. Thus, treatment of each atropisomer of **20** with TBAF gave the diol **22** which did not show any atropisomerism. Diol **23** {$[\alpha]_D$ +23.0 (*c* 0.10)}, obtained from both atropisomers of **21** by deprotection with TBAF, also showed no atropisomerism.

Dihydroxylation of **23** followed by hydrogenolysis of the resultant **24** {$[\alpha]_D$ − 68.1 (*c* 0.32)} with $Pd(OH)_2$-C (Degussa type) in the presence of a trace amount of conc. HCl gave D-*chiro*-inositol **2**, the physical properties of which are identical with those of authentic **2**.[10] Perbenzoate **25**[11] was prepared for further characterization of **2**. A similar synthesis starting with the (1*R*,2*R*)-diasteromer of **3** would provide L-*chiro*-inositol. The development of the highly diastereoselective oxyselenenylation of cyclohexene with various chiral alcohols including hydrobenzoin derivatives is now in progress.

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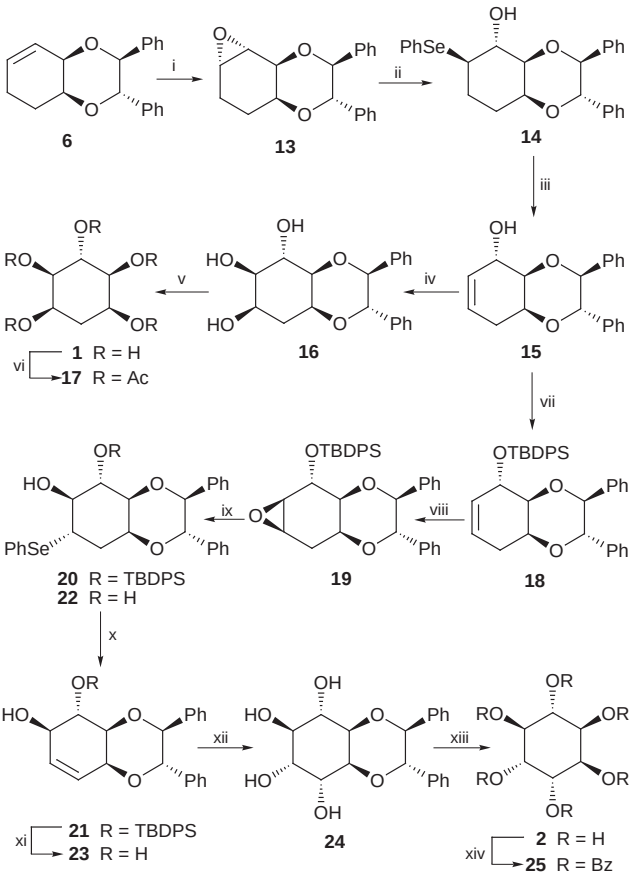

Scheme 2 *Reagents and conditions*: i, MCPBA, $NaHCO_3$, CH_2Cl_2, reflux, 16 h, 60% of **13** and 26% of its *cis* isomer; ii, PhSeSePh, $NaBH_4$, EtOH, reflux, 4 h, 95%; iii, 30% H_2O_2, THF–EtOH, room temp., then reflux, 6 h, 96%; iv, $K_2OsO_4H_2O$ (cat.), NMO, acetone–H_2O, reflux, 20 h, 92%; v, H_2, $Pd(OH)_2$ (cat.), conc. HCl (trace), EtOH, 15 psi, room temp., 1 h, 93%; vi, Ac_2O, pyridine, room temp., 12 h, 85%; vii, TBDPSCl, imidazole, DMF, reflux, 14 h, 87%; viii, MCPBA, $NaHCO_3$, CH_2Cl_2, reflux, 20 h, 51% of **19** and 34% of its *cis* isomer; ix, PhSeSePh, $NaBH_4$, Bu^{n}OH, reflux, 24 h, 83% (a mixture of two atropisomers, 3:2); x, $NaIO_4$, $NaHCO_3$, MeOH–H_2O, room temp., 10 min, then 90 °C, 48 h, 90% (a mixture of two atropisosmers, 3:2); xi, Bu$^n{}_4$NF, THF, room temp., 5 h, 92%; xii, $K_2OsO_4H_2O$ (cat.), NMO, acetone–H_2O, reflux, 18 h, 87%; xiii, H_2, $Pd(OH)_2$ (cat.), conc. HCl (trace), EtOH, 15 psi, room temp., 1 h, 82%; xiv, BzCl, pyridine, 12 h, room temp., 86%

Notes and References

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‡ *Selected data* for **3**: colourless glass (Found: C, 69.16; H, 6.42. $C_{26}H_{28}O_2Se$ requires C, 69.17; H, 6.25%); R_f = 0.27 (silica gel, hexane–EtOAc, 7:1); $[\alpha]_D$ +4.2 (*c* 0.55, CH_2Cl_2); δ_H(500 MHz; $CDCl_3$) 1.20–1.36 (2 H, m), 1.39–1.52 (2 H, m), 1.53–1.63 (1 H, m), 1.65–1.73 (1 H, m), 2.02–2.10 (1 H, m), 2.12–2.19 (1 H, m), 3.31–3.37 (1 H, m), 3.39–3.45 (2 H, m), 4.37 and 4.62 (2 H, ABq, *J* 8.1), 6.96–7.01 (2 H, m), 7.07–7.22 (11 H, m), 7.36–7.40 (2 H, m). For (1*R*,2*R*)-diastereomer of **3**: white solid, mp 60–62 °C; R_f = 0.37 (silica gel, hexane–EtOAc, 7:1); $[\alpha]_D$ −79.5 (*c* 1.48, CH_2Cl_2); δ_H(500 MHz; $CDCl_3$) 1.02–1.14 (2 H, m), 1.16–1.28 (1 H, m), 1.41–1.62 (3 H, m), 1.64–1.72 (1 H, m), 2.14–2.21 (1 H, m), 3.21–3.28 (1 H, m), 3.44–3.50 (1 H, m), 4.26 and 4.68 (2 H, ABq, *J* 8.7), 4.72–4.80 (1 H, s), 6.92–6.94 (2 H, m), 6.92–7.02 (2 H, m), 7.12–7.19 (6 H, m), 7.29–7.32 (3 H, m), 7.68–7.72 (2 H, m).

§ Unlike the first oxyselenenylation step, the intramolecular oxyselenenylation proceeded in a reasonable yield only with PhSeOTf, possibly because other selenium reagents, including *N*-PSP, are not reactive enough for the intramolecular oxyselenenylation.

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