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LETTERS

Synthesis of Enantiopure Cyclopentitols and Aminocyclopentitols Mediated by Oxyselenenylation of Cyclopentene with (*R*,*R*)-Hydrobenzoin

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Dedicated to Professor E. J. Corey on the occasion of his 70th birthday.

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Abstract: Oxyselenenylation of cyclopentene with (*R*,*R*)-hydrobenzoin and subsequent oxidation-elimination of the resulting oxyselenide **1** afforded olefin **2**. Intramolecular oxyselenenylation of **2** occurred in a completely regio- and stereoselective manner to give oxyselenide **3**. Further transformation of **2** and **3** provided enatiomerically pure cyclopentanetriol **7**, cyclopentanetetrol **9**, aminocyclopentitol **15**, and cyclopentitol **19**. © 1998 Elsevier Science Ltd. All rights reserved.

A great deal of efforts has been made for the synthesis of highly substituted cyclopentanes since they were frequently found as the integral parts of many important natural products. Recently, cyclopentitols, polyhydroxylated cyclopentanes, have been the focus of much attention from synthetic chemists mainly because aminocyclopentitols such as allosamidin,[1] mannostatin,[2] trehalostatin,[3] and trehazolin,[4] have been recognized as strong glycosidase inhibitors. These naturally occurring inhibitors and their synthetic analogs are in great value as the tool for basic biochemical research and as the potential therapeutic agents.[5] Although several methods are available for the synthesis of these cyclopentitols,[6] there still remains a need for the new methodology starting from the simple starting material like cyclopentene. Efficient methodology for the transformation of cyclopentene to enantiopure cyclopentitols would be in great value not only because of the aforementioned reason but also because it can be applied for the synthesis of many other highly substituted cyclopentanes. However, the enantioselective functionalization of cyclopentene poses the challenge: asymmetric epoxidation or dihydroxylation of cyclopentene, for example, can not be employed. Herein we report the synthesis of enantiopure cyclopentitols starting from cyclopentene by serial oxyselenenylation.

To a solution of *N*-(phenylseleno)phthalimide (*N*-PSP)[7] (5.02 mmol), (*R*,*R*)-hydrobenzoin (6.53 mmol), and cyclopentene (12.06 mmol) in methylene chloride (50 ml) was added slowly $BF_3 \cdot OEt_2$ (0.50 mmol) at 0 °C. Stirring the reaction mixture at 0 °C for 45 min and at room temperature for further 2 h afforded (1*R*,2*R*)-oxyselenide **1** and its (1*S*,2*S*)-diastereomer in about 1 : 1 ratio in 75% yield (Scheme 1). The mixture of **1** and its diastereomer, without separation,[8] was oxidized with $NaIO_4$ and subsequent elimination of the resulting selenoxide provided olefin **2** and its (1*S*)-diastereomer in 1 : 1 ratio in 92% yield. After separation from its diastereomer by column chromatography,[9] compound **2** was treated with PhSeOTf,[10] which was generated *in situ* from PhSeBr and AgOTf, to give only *cis* fused bicyclic dioxane **3**. The fact that the intramolecular oxyselenenylation of allylic alcohol derivative **2** occurred in a completely regio- and stereoselective manner to

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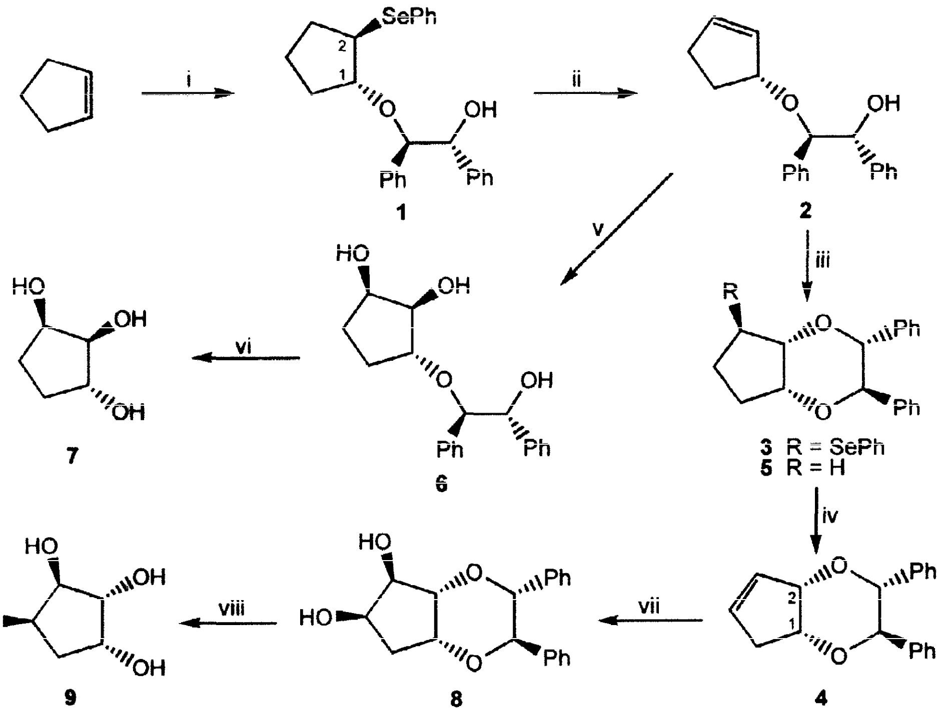
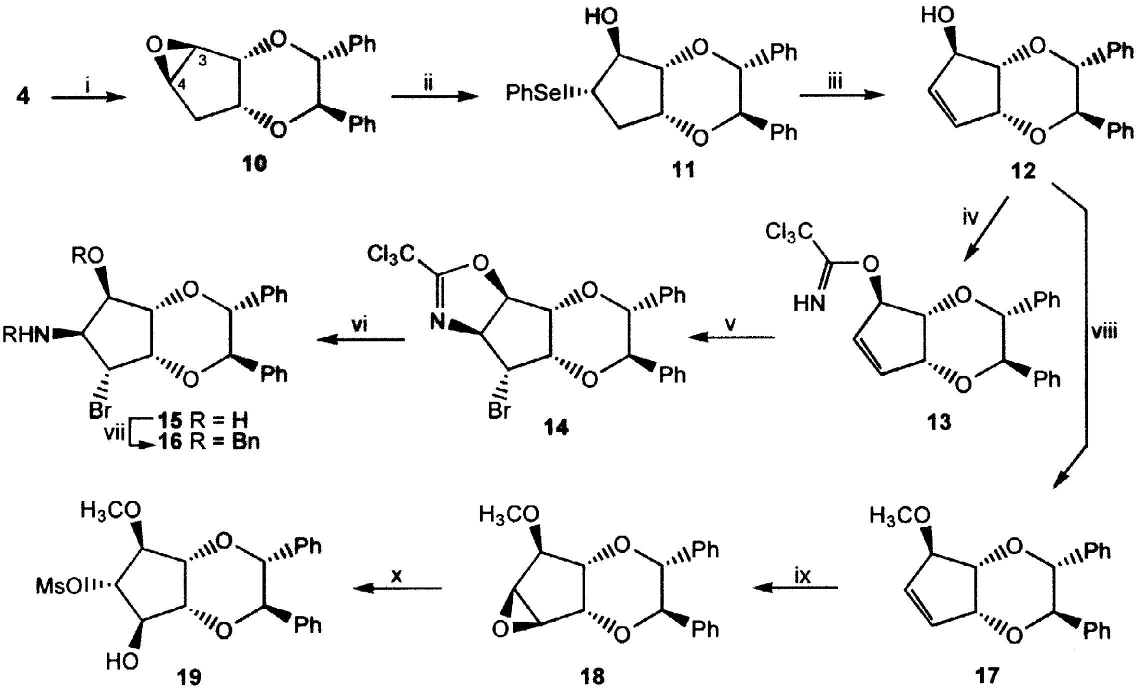
give 1,2-*cis* diol derivative **3** is noteworthy since the oxyselenenylation of cyclic[11] and acyclic[12] allylic alcohol derivatives give 1,3-*anti* diol derivative. Compound **3**, without isolation from the reaction mixture,[13] was oxidized with $NaIO_4$ in the presence of $NaHCO_3$ and subsequent elimination of the resulting selenoxide gave olefin **4**[14] in 70% yield from compound **2**.

The absolute configuration of compounds **2** and **4** was established on the basis of the physical and spectroscopic data of compounds **5** and **7**. Thus, dihydroxylation of **2** with OsO_4 and *N*-mthylmorpholine *N*-oxide (NMO) afforded compound **6** which was further transformed to the known cyclopentanetriol **7**[15] by hydrogenolysis. The absolute configuration of **2** was, therefore, assigned as *R*. Reduction of selenide **3** with tributyltin hydride gave compound **5** of which ^1H NMR spectrum clearly indicated that its bicyclic ring was *cis*-fused. Consequently, C1 and C2 configurations of 3-cyclopentene-1,2-diol derivative **4** were unambiguously determined to be *R* and *S*, respectively. Dihydroxylation of **4** with OsO_4 and NMO and subsequent hydrogenolysis of the resulting diol **8** gave cyclopentanetetrol **9**[16] in high yield.



Scheme 1. *Reagents and conditions:* i, (*R,R*)-hydrobenzoin, *N*-PSP, cat. BF_3OEt_2, CH_2Cl_2, 0°C, 45 min, then RT, 2 h, 75% of **1** and its (1*S*,2*S*) -diastereomer; ii, $NaIO_4$, $NaHCO_3$, MeOH/ H_2O, RT, 10 min, then reflux, 48 h, 92% of **2** and its (1*S*)-diastereomer, separation of two diastereomers by column chromatography; iii, PhSeOTf, CH_2Cl_2, -78°C to RT, 2 h; iv, $NaIO_4$, $NaHCO_3$, MeOH/ H_2O, RT, 10 min, then reflux, 48 h, 70% from **2**; v, cat. OsO_4, NMO, acetone/ H_2O, RT, 24 h, 66%; vi, H_2, Pd-C, EtOH, 50 psi, RT, 8 h, 80%; vii, cat. $K_2OsO_4H_2O$, NMO, acetone/H_2O, reflux, 20 h, 92%; viii, H_2, Pd-C, EtOH, 50 psi, RT, 8 h, 98%.

The reaction of olefin **4** with *m*-chloroperbenzoic acid (mCPBA) provided only *trans*-epoxide **10** in 91% yield (Scheme 2). Treatment of **10** with sodium phenylselenide, obtained from diphenyldiselenide with $NaBH_4$, resulted in cleavage of epoxide ring only at C-4 to give hydoxyselenide **11**. Complete stereoselectivity in epoxidation of **4** and regioselectivity in epoxide ring opening of **10** must be steric origin due to the bulky diphenyldioxane ring. Oxidation of **11** with H_2O_2 followed by selenoxide elimination led to allylic alcohol **12** in 86% yield. In order to generate the vicinal *cis*-aminohydroxyl group found in most of naturally occurring



Scheme 2. *Reagents and conditions*: i, mCPBA, $NaHCO_3$, CH_2Cl_2, reflux, 48 h, 91%; ii, PhSeSePh, $NaBH_4$, EtOH, reflux, 3 h, 89%; iii, H_2O_2, THF/EtOH, 60 h, 86%; iv, CCl_3CN, DBU, CH_2Cl_2, reflux, 3 h, 91%; v, Br(*sym*-collidine)$_2$ClO$_4$, CH_2Cl_2, reflux, 18 h, 60%; vi, 2 M HCl, MeOH, 1 h; vii, BnBr, Bu_4NI, NaH, THF, RT, 16 h, 43% from **14**; viii, MeI, NaH, THF, 0°C to RT, 96%; ix, mCPBA, $NaHCO_3$, CH_2Cl_2, reflux, 48 h, 82%; x, MsOH,CH_2Cl_2, reflux, 74%.

aminocyclopentitol-containing glycosidase inhibitors, compound **12** was treated with trichloroactonitrile and DBU to yield trichloroimidate**13** in 91% yield. Compound **13** was cyclized upon treatment with Br(*sym*-collidine)$_2$ClO$_4$ to afford compound **14** in 60% yield whereas I(*sym*-collidine)$_2$ClO$_4$ was not effective for the cyclization of **13**. Acid hydrolysis of **14** afforded an aminocyclopentitol **15**, which was converted into benzyl ether **16**[17] containing vicinal *cis*-aminohydroxyl group. Compound **12** was also transformed to epoxide **18** and mesylate **19**, which could be the useful precursors for the synthesis of aminocyclitols such as allosamidin, mannostatin, trehalostatin, and trehazolin. Thus, compound **12** was subjected to standard methylation condition with methyl iodide to yield **17**, of which epoxidation with mCPBA afforded epoxide **18** exclusively in 82% yield. Epoxide ring opening of **18** with MsOH provided mesylate **19**[18] in 74% yield. Again stereochemistry of epoxidation of **17** and regiochemistry of ring opening of **18** were completely controlled by *cis*-fused bulky diphenyldioxane ring. The similar synthesis starting from (1*S*)-diastereomer of **2** would provide another series of cyclopentitols. We are currently pursuing the total synthesis of trehalostatin by employing the present methodology.

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6. For example, see: (a) Ledford, B. E.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 11811-11812. (b) Kobayashi, Y.; Miyazaki, H.; Shiozaki, M. *J. Org. Chem.* **1994**, *59*, 813-822. (c) Trost, B. M.; Vranken, D. L. V. *J. Am. Chem. Soc.* **1993**, *115*, 444-458.
7. Other selenium reagents such as PhSeCl, PhSeBr, and PhSeOTf frequently generated the undesired haloselenide or hydroxyselenide.
8. Separation of diastereomeric selenides is much more difficult despite of their different R_f values than nonselenides. Compound **1**: R_f 0.24 (silica gel, hexane/EtOAc = 7/1). (1*S*,2*S*)-Diastereomer of **1**: R_f 0.26.
9. Compound **2**: mp 61-63 °C; R_f 0.32 (silica gel, hexane/EtOAc = 7/1); $[\alpha]^{20}_{D}$ +23.5 (*c* 1.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.85-1.97 (m, 1 H), 2.11-2.32 (m, 2 H), 2.49-2.62 (m, 1 H), 3.57 (brs, 1 H), 4.36 and 4.67 (ABq *J* = 8.1 Hz, 2 H), 4.54-4.58 (m, 1 H), 5.64 (dd, 5.6, 2.1 Hz, 1 H), 5.99-6.02 (m, 1 H), 7.06-7.09 (m, 4 H) 7.20-7.29 (m, 6 H). (1*S*)-Diastereomer of **2**: mp 68-70 °C; R_f 0.33; $[\alpha]^{20}_{D}$ –62.6 (*c* 0.86, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.73-1.86 (m, 1 H), 1.95-2.09 (m, 1 H), 2.18-2.28 (m, 1 H), 2.43-2.57 (m, 1 H), 3.61 (s, 1 H), 4.36 and 4.64 (ABq, *J* = 8.3 Hz, 2 H), 4.56-4.60 (m, 1 H), 5.98-6.02 (m, 1 H), 6.08-6.12 (m, 1 H), 7.05-7.10 (m, 4 H), 7.17-7.30 (m, 6 H). All new compounds gave satisfactory spectroscopy and/or microanalytical data.
10. Unlike the oxyselenenylation of cyclopentene at the first step, *N*-PSP gave a poor result in the intramolecular oxyselenenylation.
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13. Although selenide **3** could be isolated as a pure form, a substantial amount of **3** was lost during purification by column chromatography on silica gel.
14. Compound **4**: mp 81-84 °C; R_f 0.42 (silica gel, hexane/EtOAc = 7/1); $[\alpha]^{20}_{D}$ +210.7 (*c* 1.38, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.35-2.42 (m, 1 H), 2.88-2.94 (m, 1 H), 4.29 (d, *J* = 8.7 Hz, 1 H), 4.33-4.45 (m, 1 H), 4.48-4.56 (m, 1 H), 4.58 (d, *J* = 8.7 Hz, 1 H), 5.92-5.98 (m, 1 H), 6.13-6.19 (m, 1 H), 6.91-7.10 (m, 10 H).
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16. Compound **9**: R_f 0.23 (silica gel, CH_2Cl_2/MeOH = 3/1); $[\alpha]^{20}_{D}$ -15 (*c* 0.56, EtOH); ^{1}H NMR (DMSO) δ 1.75 (brs, 2 H), 3.64 (brs, 2 H), 3.94 (brs, 2 H) 4.31 (s, 2 H), 4.66 (s, 2 H).
17. Compound **16**: R_f 0.29 (silica gel, hexane/EtOAc = 6/1); ^{1}H NMR ($CDCl_3$) δ 3.76-3.84 (m, 2 H), 4.00-4.08 (m, 2 H), 4.29 (dd, *J* = 4.7, 0.9 Hz, 1 H), 4.35 and 4.45 (ABq, *J* = 8.9 Hz, 2 H), 4.64 and 4.70 (ABq, *J* = 12.3 Hz, 2 H), 4.90 (dd, *J* = 7.8, 4.7 Hz, 1 H), 5.05 (t, *J* = 4.7 Hz, 1 H), 6.83-7.42 (m, 20 H).
18. Compound **19**: R_f 0.33 (silica gel, hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 3.01 (brs, 1 H), 3.09 (s, 3 H), 3.45 (s, 3 H), 3.68 (d, *J* – 4.2 Hz, 1 H), 4.07-4.21 (m, 2 H), 4.40 (dd, *J* = 9.5, 4.8 Hz, 1 H), 4.49 and 4.78 (ABq, *J* = 9.2 Hz, 2 H), 5.65 (dd, *J* = 9.5, 7.2 Hz, 1 H), 6.97-7.06 (m, 4 H), 7.15-7.25 (m, 6 H).