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Synthesis of (+)-polyoxamic acid and D-sorbitol from simple achiral allylic halides employing (*S*,*S*)-hydrobenzoin as a chiral source

Kwan Soo Kim,* Yong Joo Lee, Jin Hwan Kim and Da Kyung Sung
Department of Chemistry, Yonsei University, Seoul 120-749, Korea. E-mail: kwan@yonsei.ac.kr; Fax: 82-2-364-7050; Tel: +82-2-2123-2640

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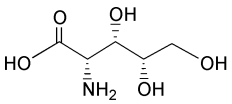
Coupling of *cis*-1-bromo-2-pentene and (*S*,*S*)-hydrobenzoin stannylene acetal followed by regio- and stereoselective transformations of the resulting allylic ether gave (+)-polyoxamic acid and a similar procedure was applied to the synthesis of D-sorbitol from *trans*-1-iodo-2-hexene.

An efficient methodology for the transformation of simple achiral acyclic allylic halides to chiral acyclic polyhydroxy or aminopolyhydroxy compounds without the carbon–chain elongation would be of great value for the synthesis of various important natural products. We have previously reported the synthesis of enantiopure cyclic polyhydroxy and aminopolyhydroxy compounds from achiral cycloalkenes using hydrobenzoin as a chiral source.[1] However, the synthesis of chiral acyclic polyhydroxy and aminopolyhydroxy compounds from simple acyclic achiral starting materials by acyclic stereocontrol poses a greater challenge. One of the most interesting acyclic aminopolyhydroxy compounds is (+)-polyoxamic acid (**1**), the side chain moiety of peptidyl nucleoside antibiotics, polyoxins,[2] which inhibit chitin synthetase of *Candida albicans*, a human fungal pathogen and of various phytopathogenic fungi as well and thus have been used as agricultural fungicides.[3] Most synthetic approaches to (+)-polyoxamic acid have used chiral starting materials[4] except Trost's work mediated by Pd-catalyzed asymmetric induction with achiral acyclic allylic substrates.[5] Herein we report a new and efficient synthesis of an acyclic aminopolyhydroxy compound (+)-polyoxamic acid (**1**) starting from 1-bromo-2-pentene employing (*S*,*S*)-hydrobenzoin not only as a chiral source but also as the oxygen atom source. We also report the synthesis of an acyclic polyhydroxy target molecule, D-sorbitol (**2**)[6] from 1-iodo-2-hexene employing the same methodology.



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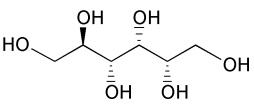

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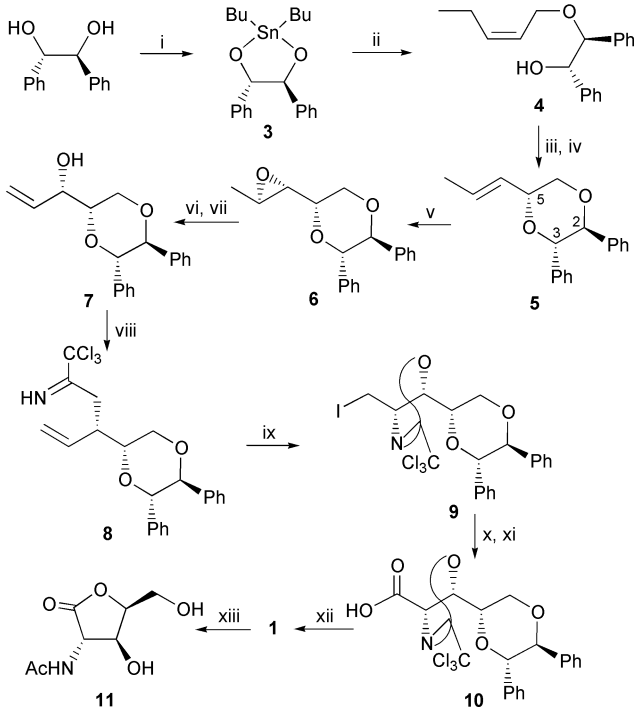
Synthesis of (+)-polyoxamic acid commenced with the coupling of *cis*-1-bromo-2-pentene and the (*S*,*S*)-hydrobenzoin stannylene acetal **3**. Direct reaction of *cis*-1-bromo-2-pentene with the sodium monoalkoxide of (*S*,*S*)-hydrobenzoin, however, gave not only the desired allylic ether **4** but also a substantial amount of the diallylic ether, which was the adduct of one mole of (*S*,*S*)-hydrobenzoin and two moles of *cis*-1-bromo-2-pentene. (*S*,*S*)-Hydrobenzoin[7] was, therefore, converted into the (*S*,*S*)-hydrobenzoin stannylene acetal **3** by its reaction with dibutyltin oxide in refluxing methanol for 30 min[8] and the crude stannylene acetal **3** was used for the next step without purification (Scheme 1). Displacement reaction of *cis*-1-bromo-2-pentene with the compound **3** in DMF afforded the allylic ether **4**. Intramolecular oxyselenenylation of the compound **4** using PhSeOTf, which was generated *in situ* from PhSeBr and AgOTf, provided an inseparable mixture of two diastereomeric oxyselenides in 92% yield. Oxidation of the oxyselenides with $NaIO_4$ in the presence of $NaHCO_3$ followed by elimination of the resulting selenoxide afforded the (2*S*,3*S*,5*S*)-olefin **5** {$[\alpha]_D$ +18 (*c* 1.0)} and its (2*S*,3*S*,5*R*)-diastereomer (3:1 ratio), which could then be separated by flash column chromatography. Attempts to direct conversion of compound **4** by oxypalladation into compound **5** under various conditions were not successful. Epoxidation of the major olefin **5** with dimethyldioxirane (DMD) was stereoselective to give the epoxide **6** {$[\alpha]_D$ –35 (*c* 1.0)} and its diastereomeric epoxide in the ratio of 9:1, which were separated by flash column chromatography. Ring opening of the major epoxide **6** with PhSeNa, generated *in situ* from PhSeSePh and $NaBH_4$, was completely regioselective to give only one hydroxyselenide, whereupon oxidation with $NaIO_4$ in the presence of $NaHCO_3$ followed by elimination provided the allylic alcohol **7** {$[\alpha]_D$ +15 (*c* 1.0)}. Treatment of the compound **7** with trichloroacetonitrile in the presence of DBU produced the trichloroacetimidate **8** {$[\alpha]_D$ +5.0 (*c* 1.0)}. Regioselective iodocyclization of the compound **8** with iodine in THF afforded iodo-1,3-oxazoline **9** {$[\alpha]_D$ +28 (*c* 1.0)}. Transformation of the iodide **9** into the alcohol was carried out by treatment of **9** with Amberlite®IRA-900 carbonate form[9] in refluxing benzene.



Scheme 1 *Reagents and conditions*: i, Bu^n_2SnO, MeOH, reflux, 30 min; ii, *cis*-1-bromo-2-pentene, DMF, rt, 8 h, 91% in 2 steps; iii, PhSeOTf, CH_2Cl_2–THF, −78 °C, 2 h, then rt, 1 h, 92%; iv, $NaIO_4$, $NaHCO_3$, MeOH–H_2O, rt, 10 min, then 70 °C, 5 h, **5** and its (2*S*,3*S*,5*R*)-diastereomer (3:1), 90%; v, DMD, acetone, rt, 2 h, **6** and its diastereomeric epoxide (9:1), 83%; vi, PhSeSePh, $NaBH_4$, EtOH, 60 °C, 2 h, 85%; vii, $NaIO_4$, $NaHCO_3$, MeOH–H_2O, rt, 10 min, then 70 °C, 48 h, 80%; viii, CCl_3CN, DBU, CH_2Cl_2, reflux, 3 h, 82%; ix, I_2, THF, rt, 3 h; 75%; x, Amberlite® IRA-900 carbonate form, benzene, reflux, 4 h, 81%; xi, $RuCl_3{\cdot}xH_2O$ (cat.), $K_2S_2O_8$, 1 M KOH, H_2O, rt, 7 h, 81%; xii, H_2, $Pd(OH)_2$ (cat.), conc. HCl (trace), EtOH, 50 psi, rt, 24 h; xiii, Ac_2O, MeOH, rt, 38% in 2 steps.

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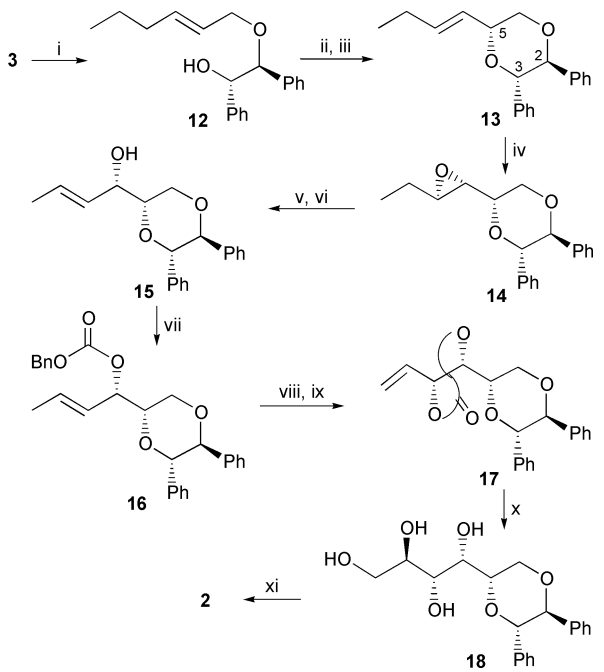
Oxidation of the resulting alcohol with $RuCl_3/K_2S_2O_8$ provided the carboxylic acid **10** {$[\alpha]_D$ +5.0 (*c* 1.0)}. Hydrogenolysis of the compound **10** using $Pd(OH)_2$ as the catalyst in the presence of a trace amount of conc. HCl gave crude (+)-polyoxamic acid (**1**), of which lactonization using acetic anhydride afforded the known lactone **11** {$[\alpha]_D$ –103 (*c* 1.0)}.[4a,h,k]

Synthesis of D-sorbitol was carried out in a similar manner (Scheme 2). Reaction of *trans*-1-iodo-2-hexene with the compound **3** in DMF afforded the allylic ether **12** {$[\alpha]_D$ –53 (*c* 2.0)}. Intramolecular oxyselenenylation of the compound **12** with PhSeOTf gave a mixture of two diastereomeric oxyselenides. Oxidation of the diastereomeric oxyselenides with $NaIO_4$ in the presence of $NaHCO_3$ followed by elimination of the resulting selenoxide provided a mixture of (2*S*,3*S*,5*S*)-olefin **13** {$[\alpha]_D$ +13 (*c* 1.0)} and its (2*S*,3*S*,5*R*)-diastereomer in the ratio of 7 : 3, which could be separated by flash chromatography. Epoxidation of the major olefin **13** with DMD proceeded in a stereoselective manner to give a separable mixture of the epoxide **14** {$[\alpha]_D$ +33 (*c* 1.0)} and its diastereomeric epoxide in the ratio of 9 : 1. Ring opening of the major epoxide **14** with PhSeNa was completely regioselective to give only one hydroxyselenide. Oxidation of the hydroxyselenide with $NaIO_4$ followed by elimination of the resultant selenoxide provided the allylic alcohol **15** {$[\alpha]_D$ +18 (*c* 1.0)}. Treatment of the compound **15** with Bu^n Li and then with benzyl chloroformate afforded the carbonate **16** {$[\alpha]_D$ +23.4 (*c* 1.5)}. Intramolecular oxyselenenylation of **16** with PhSeBr and the subsequent oxidation of the resultant selenenyl cyclic carbonate followed by elimination of the resulting selenoxide gave the olefinic cyclic carbonate **17** {$[\alpha]_D$ –23 (*c* 1.0)}. Dihydroxylation of olefin **17** with OsO_4/NMO afforded the diol, of which cyclic carbonate group was hydrolysed during the workup process to afford the tetrol **18** {$[\alpha]_D$ –29 (*c* 1.0)}. Hydrogenolysis of the compound **18** using $Pd(OH)_2$ as the catalyst gave D-sorbitol (**2**).



Scheme 2 *Reagents and conditions*: i, *trans*-1-iodo-2-hexene, DMF, rt, 8 h, 95%; ii, PhSeOTf, CH_2Cl_2–THF, −78 °C, 2 h, then rt, 1 h, 93%; iii, NaIO4, $NaHCO_3$, MeOH–H_2O, rt, 10 min, then 70 °C, 5 h, **13** and its (2*S*,3*S*,5*R*)-diastereomer (7 : 3), 91%; iv, DMD, acetone, rt, 2 h, **14** and its diastereomeric epoxide (9 : 1), 82%; v, PhSeSePh, $NaBH_4$, EtOH, 60 °C, 2 h, 88%; vi, $NaIO_4$, $NaHCO_3$, MeOH–H_2O, rt, 10 min, then CCl_4, 70 °C, 12 h, 85%; vii, Bu^nLi, THF, −78 °C, 5 min, then benzyl chloroformate, −78 °C, 1 h, 98%; viii, PhSeBr, CH_3CN, 60 °C, 24 h, 62%; ix, $NaIO_4$, $NaHCO_3$, MeOH–H_2O, rt, 10 min, then 70 °C, 48 h, 87%; x, OsO_4 (cat.), NMO, acetone–H_2O, 60 °C, 48 h, 60%, xi, H_2, $Pd(OH)_2$ (cat.), conc. HCl (trace), EtOH, 50 psi, rt, 24 h, 68%.

In conclusion, we demonstrated that the present methodology employing (*S*,*S*)-hydrobenzoin as the chiral source and as the oxygen source would be very useful for the synthesis of important acyclic aminopolyhydroxy and polyhydroxy compounds from simple achiral substances. Another merit of the present methodology is that an identical procedure using (*R*,*R*)-hydrobenzoin would provide the enantiomers of those obtained using (*S*,*S*)-hydrobenzoin.

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